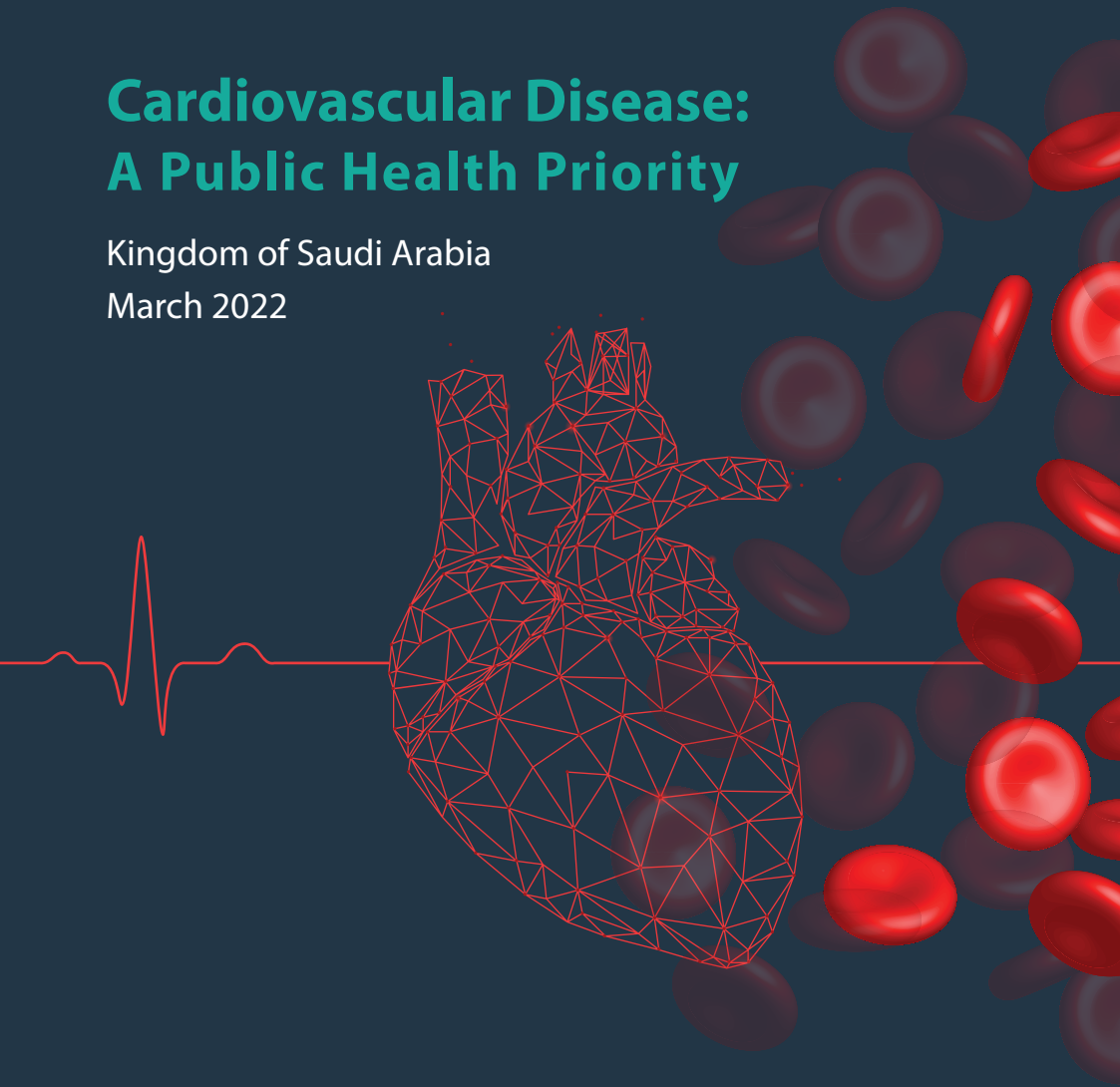
المركز الوطني للقلب
National Heart Center

المجلس الصحي السعودي
Saudi Health Council

Cardiovascular Disease: A Public Health Priority

Kingdom of Saudi Arabia
March 2022



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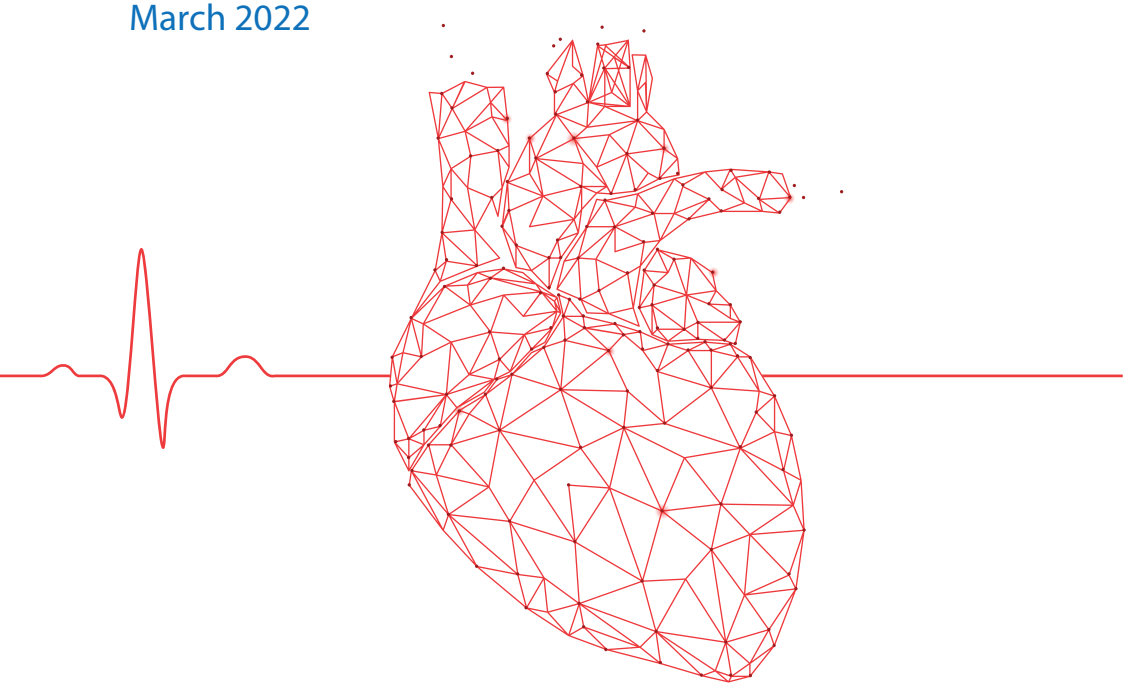

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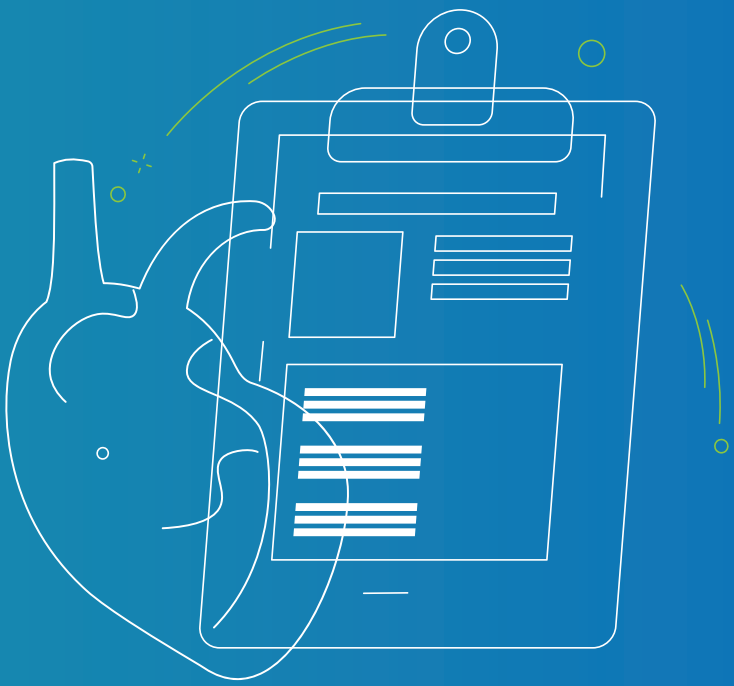
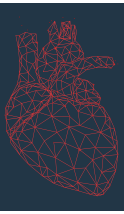


Executive summary

Cardiovascular disease (CVD) includes a range of presentations, such as stable or unstable angina, stroke or myocardial infarction (3). CVD risk factors are commonly understood to include lifestyle factors such as smoking, lack of exercise, high blood pressure (hypertension), elevated cholesterol and diabetes. Focusing on reducing risk through modifiable risk factors, such as high blood pressure, smoking and elevated cholesterol, can have substantial benefits in reducing the incidence of CVD and related events (4).

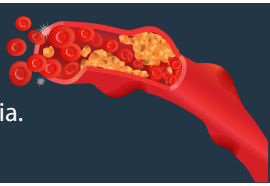


There is an urgent need to address CVD in the Kingdom of Saudi Arabia. Public health strategies across the whole population will deliver far reaching benefits for this and future generations.

Over 30 percent of adults (18 years) in the Kingdom of Saudi Arabia (KSA) are at risk of a CVD event (7 ,8). In KSA, CVD is associated with smoking, consumption of high fatty food and low fibre intake, and sedentary lifestyle. Many people also have a range of other comorbid conditions or risks, such as diabetes mellitus (12.3 percent), smoking (16 percent), hypertension (22 percent), and high cholesterol or dyslipidaemia (35 to 40 percent) (8 ,10 ,11) (Figure 1).

Multiple national and international multicentric studies reveal that 35 percent of the KSA population have cholesterol at levels above the recommended target (7,8,12). which Is significantly higher compared to other countries (8,13,15). In contrast, approximately 21 percent of adults in the United States have dyslipidaemia (18).

Elevated cholesterol, or dyslipidaemia is the most prevalent modifiable disease risk factor for CVD in the Kingdom of Saudi Arabia.



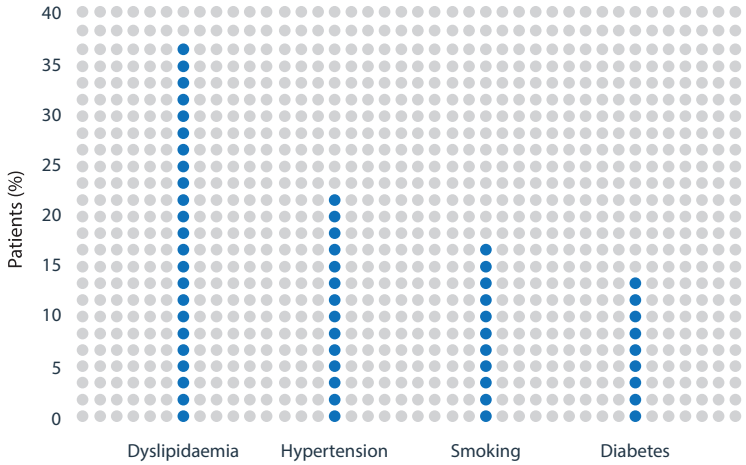


Figure 1 Prevalence of CVD risk factors in KSA

The impact of CVD

The impact of CVD in terms of non-fatal events and death is stark. In KSA, 42 percent of all deaths are attributed to CVD (21). The number of deaths resulting from ischemic heart disease and hypertensive heart disease in the Middle East is 309 per 100,000 (23) as compared to North America which has a rate of 204 per 100,000 and Western Europe which has a rate of 187 per 100,000 individuals (24). With 60 percent of the KSA population aged 35 years or younger (11), the net result is that in KSA, patients will suffer a CVD event, on average 10 years earlier when compared with the Western population (26).

The burden of CVD resulting in disability or years of healthy life lost due to disability (YLD)[1] in KSA in 2017 was 10,921 YLDs per 100,000 (11). The number of disability-adjusted life years (DALYs)[2] from ischemic and hypertensive heart disease in KSA is 3,702 per (11) 100,000 (23 ,27).

[1] YLD can be described as the number of years that were spent in less than full health as compared to years that could have been spent living a health life. In essence, YLD is a representation of non-fatal burden. Years of life cost can be described as the numbers of years lost due to dying before the ideal life span i.e. premature (early) death

[2] DALY can be described as measure of overall disease burden. DALY is a representation of the number of years lost due to poor health, disability or premature (early) death. DALY is calculated by adding YLD + YLL. YLL is defined as the reduction in life expectancy and is calculated by multiplying the standard life expectancy at age of death (L1) and the number of deaths (n).

The Framingham Risk Score is commonly used to calculate CVD risk. One study showed that in KSA, patients with the highest risk of CVD are in the 61 - 75 year age group, with a prevalence of around 49 percent. Of the moderate to high risk patients, there is a larger prevalence amongst males in KSA at around 33 percent compared with 17 percent of females (28).

CVD in KSA is expected to increase by approximately 480,000 people by the year 2035, with a threefold increase in economic burden (SAR 36.75 billion; USD 9.8 billion) (26). The benefit of decreasing CVD risk through targeted policy solutions, as recommended by this report, will significantly improve the health of those living in KSA.

There is an urgent need to address CVD in the Kingdom of Saudi Arabia. Public health strategies across the whole population will deliver immense benefits for this and future generations.

CVD a public health priority

Whilst treatment at an individual patient level is important, KSA urgently need a coordinated public health approach to reduce CVD risk across the entire population. The anticipated impact of a public health program is a significant reduction in morbidity and mortality (11,12,29). Within the first five years of implementing a public health approach, as per the recommendations in this report, there will be 112,748 fewer deaths and 465,387 non-fatal CVD events avoided.

112,748
fewer deaths

465,387
non-fatal CVD events avoided

The investment in healthcare to achieve this result is an additional 11,269 SAR (USD 3,005) per patient over the five years, this includes screening tests, healthcare professional costs and lipid-lowering therapies. This investment will lead to increase in productivity of SAR 1,905 million (USD 508 million) based on the number of deaths avoided (22,550 per year) and Gross Domestic Productivity per capita in 2018 of SAR 87,514 (USD 23,337) (30).

Fewer CVD events results in less hospitalisations and an increased quality of life for KSA citizens (8). These recommendations also result in a reduction of non-fatal CVD events associated with atherosclerotic disease, namely myocardial infarction, revascularisation procedures and both ischaemic and haemorrhagic stroke (Figure 2).

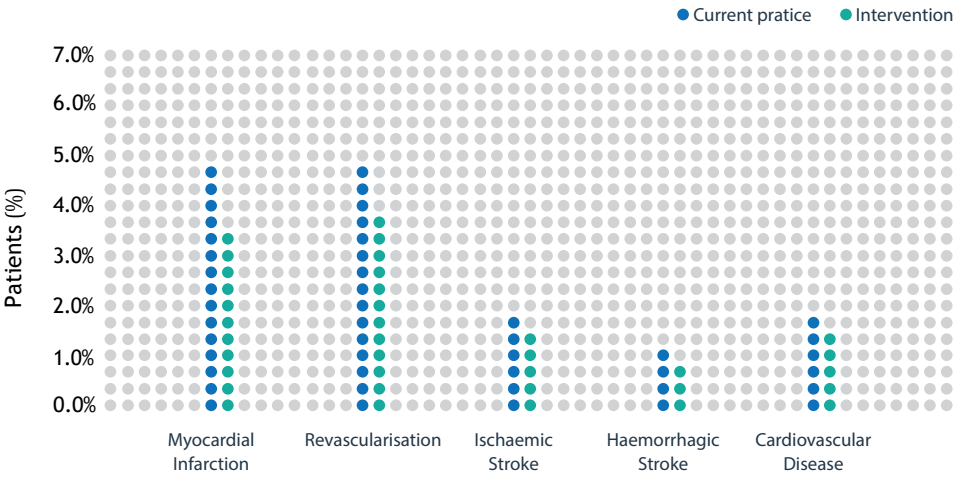


Figure 2 Reduction in CVD deaths and non-fatal events from a public health program

> Managing CVD risk, by implementing effective public health strategies, will have far reaching positive health effects on the individual as well as the entire KSA population. - **Government policy maker**

Recommendations

The public health recommendations presented below were developed through literature review, research, and interviews with key stakeholders. Input was sought from public health experts, cardiologists, family health physicians and healthcare policy makers

The seven population-level recommendations significantly reduce the risk of CVD events and associated burden of disease in the KSA population. Critically, by adopting a public health approach, these recommendations will improve the health of future generations. The seven recommendations are as follows:

01 Develop a national CVD risk screening program with multiple access points in the community.

02 Develop a region-specific CVD risk calculator.

03 Develop region-specific CVD guidelines along with quality indicators to monitor implementation and impact.

04 Develop a CVD digital dashboard to monitor risk, quality indicators and impact of guidelines.

05 Develop a CVD course targeted at family health physicians.

06 Enhance the role and education of other healthcare professionals in screening and monitoring of patients with CVD.

07 Develop targeted public health awareness campaign that includes:

- The importance of screening for CVD risk.
- Patient education materials focused on treatment options and medication compliance.

There is an opportunity for policy makers to commit to this multifaceted public health program to reduce the impact of CVD on the population both today and in the future.

The Public Health Approach to the Burden of CVD in KSA Results in

11,269 SAR
Additional cost Government per patient over five years

1,905,000,000 SAR
Increase in productivity over five years

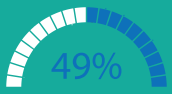
112,748 lives saved in the first five years alone + **465,387** non-fatal CVD events avoided in the first five years alone

Our recommendations result in an **EIGHT-FOLD INCREASE** of people achieving cholesterol target

92%
92 percent improvement in the number of people commencing on lipid lowering therapy

Over 30 percent of adults (⩾18 years) in the Kingdom of Saudi Arabia (KSA) are at risk of a CVD event (7 ,8)

CVD in KSA is expected to increase by approximately **480,000** people by the year 2035, with a **threefold increase** in economic burden (USD 9.8 billion) (26).



49 percent of people 61-75 years of age are categorised high risk of CVD

Non-compliance of patients to lipid lowering therapy (LLT) is common in KSA (31)

Only 28 percent of clinicians aware of appropriate LDL-C targets (32)

Almost 60 percent of patients receiving statin treatment have inadequately controlled lipid levels (14)

Abbreviations

ASCVD: Atherosclerotic Cardiovascular Disease	ACS: Acute Coronary Syndrome	ACC: American College of Cardiology	AMA: American Medical Association	BCC: Behavioural Change Communication	CVD: Cardiovascular Disease
CVA: Cerebrovascular Accident	CME: Continued Medical Education	DALY: Disability Adjusted Life Years	ESC: European Society of Cardiology	EAS: European Atherosclerosis Society	FRS: Framingham Risk Score
FH: Familial Hypercholesterolemia	HDL-C: High Density Lipoprotein Cholesterol	LLT: Lipid Lowering Therapy	LpL: Lipoprotein Lipase	LDL-C: Low Density Lipoprotein Cholesterol	MoH: Ministry of Health
NPHIES: National Platform for Health Information Exchange System	9-PCSK Inhibitors: Proprotein convertase subtilisin/kexin Inhibitors 9 type	PVD: Peripheral Vascular Disease	QALY: Quality Adjusted Life Years	RCT: Randomised Control Trial	SAR: Saudi Arabia Riyal
SEM: Socio Ecological Model	TIA: Transient Ischaemic Attack	TG: Triglycerides	UAE: United Arab Emirates	USD: United States Dollars	YLD: Years Lived with Disability
YLL: Years of Life Lost					

2 CVD - A National Health Priority

CVD - A National Health Priority

Globally, approximately 31 percent of all deaths are attributed to Cardiovascular Disease (CVD) (33). This leading cause of mortality is emerging as a significant public health concern for Middle East countries where 45 percent of all deaths have been attributed to CVD (33).

Each year in the Kingdom of Saudi Arabia (KSA), 294 per 100,000 popeletion die from CVD (23 ,33), with a further 3,702 per 100,000 popeletion non-fatal CVD events, which includes the number of disability-adjusted life years (DALYs) resulting from both hypertensive and ischemic heart disease (11).

A higher prevalence of multiple risk factors for CVD has been found in KSA compared to the United States (24) and European countries (34). These CVD risk factors include ischaemic heart disease (23.3 percent), hypertension (22 percent), history of stroke (16 percent), smoking (16 percent), diabetes mellitus (12.3 percent) and dyslipidaemia (35 percent) (,10 ,31 ,35 8). Dyslipidaemia, is the clinical term for elevated cholesterol (see Box – What is cholesterol?).

In addition, 60 percent of the population in KSA is aged 35 or younger (33). This has implications for KSA as within the Gulf region, people generally present with CVD at a much younger age compared to those in other countries (36).

There is an increased prevalence of CVD as high as 30-40% percent due to lifestyle, co-morbid conditions including diabetes, obesity and hypertension.
Family physician in KSA

Healthcare, including CVD, is rapidly changing in KSA due to rapidly changing population dynamics (29) (See Box – Healthcare in KSA).

Effective interventions for noncommunicable diseases in KSA

The Saudi Government has, through Saudi Vision 2030 , a goal to increase life expectancy from 75 to 80 years of age (16). This will be achieved primarily by addressing the disease burden of noncommunicable diseases in the country, such as CVD.

The KSA Government recognises that these diseases are largely preventable in nature, and a reduction in associated death and morbidities can be achieved by addressing behavioural and biological risk factors. These include obesity, hypertension and elevated cholesterol. There is a particular focus on promoting lifestyle changes to younger KSA citizens, so that many of the noncommunicable diseases can be prevented and benefits accrued over many years into the future.

The Saudi Public Health Authority with World Bank Group support has produced areport- Noncommunicable Diseases in Saudi Arabia: Toward effective interventions for prevention (20). This masterplan for the prevention of public health burden is comprehensively detailed, thus providing the necessary strategic direction to minimise both the health and economic burden of diseases, such as CVD, so that an increase in life expectancy can be achieved.

Primary and secondary prevention of CVD

There are two approaches for preventing CVD – primary and secondary:

01 | Primary prevention

Primary prevention is the approach taken to prevent a CVD event before it happens. Primary prevention commonly focusses on lifestyle behaviours, including exercise and diet and medication (e.g. to lower cholesterol or blood pressure) (37).

Figure 3 indicates the importance of a population, or public health approach (38). This figure demonstrates that taking a public health approach can shift the CVD risk level distribution to the left and reduce the number of patients categorised at higher risk levels.

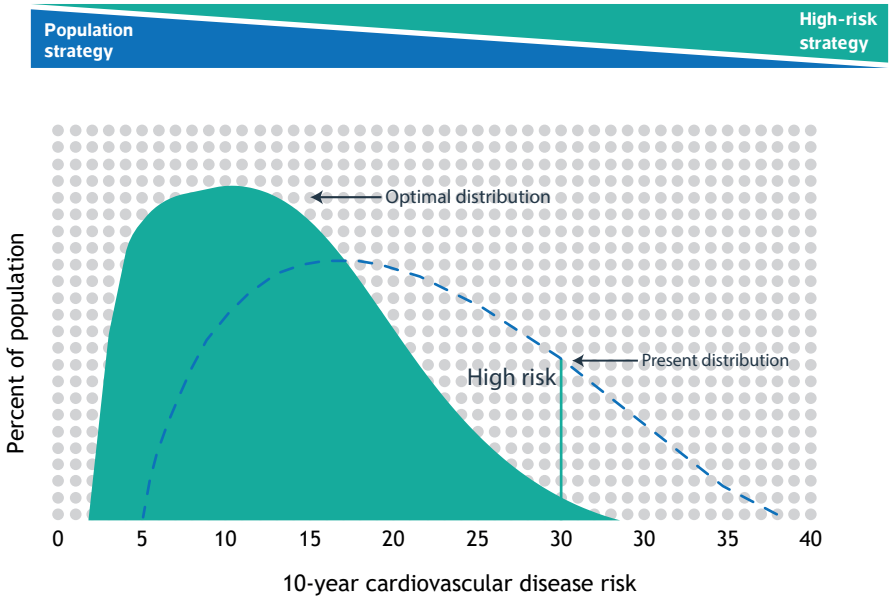


Figure 3 Reducing the CVD Burden of disease (Source: World Health Organisation) (38)

02| Secondary prevention

Secondary prevention targets patients at risk of a second, or subsequent CVD event. For example, patients with pre-existing coronary heart disease (CHD), cerebrovascular disease (CVA) or peripheral vascular disease (PVD), or at risk of a CVD event, such as myocardial infarction (MI) or stroke (37). When it comes to atherosclerotic CVD, the definitions as per the European Society of Cariology/European Atherosclerosis Society (ESC/EAS) and American College of Cardiology American Heart Association (ACC/AHA) Guidelines define patients on a spectrum of risk, from low risk through to very high risk (22 ,3) and for these patients, desired target treatment levels are specified (Appendix C).

The intensity of interventions and treatment for management of CVD risk in secondary prevention increases with CVD risk as presented in Figure 4 (38).

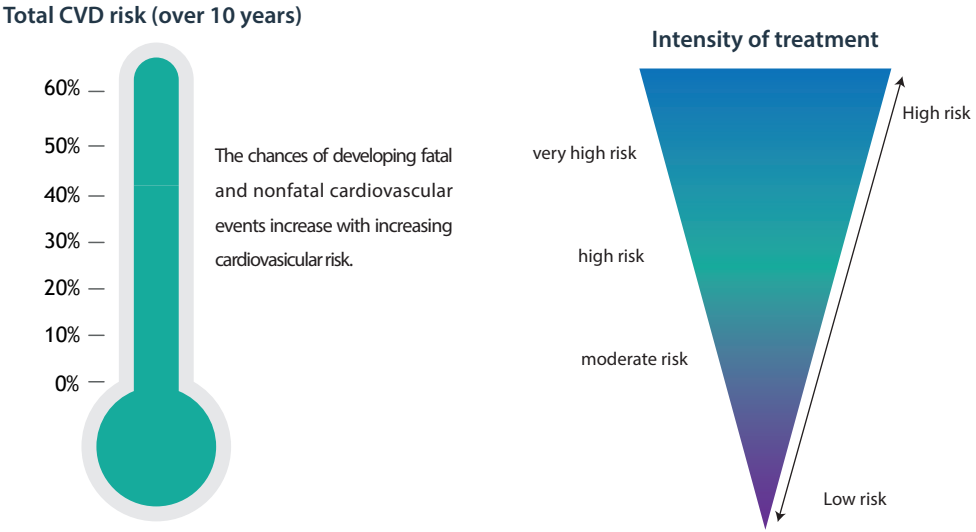


Figure 4 The importance of rigorous interventions and treatment for management of CVD risk (Source: World Health Organisation) (38)

How is CVD risk calculated?

The Framingham Risk Score (FRS) determines the likelihood (or chance) of a person developing CVD or a CVD condition, including coronary heart disease (CHD), cerebrovascular events including ischemic stroke, haemorrhagic stroke, and transient ischemic attack (TIA), PVD, stroke and heart failure (28,39). The FRS provides an estimate of a person's absolute risk of CVD over the next ten years based upon age, gender, total cholesterol, HDL level, systolic blood pressure, diabetes status and smoking behaviour (39,40). A person's FRS score is commensurate with their level of CVD risk, examples include:

- a person with a low score (< 10) has less than 10 percent risk of developing CVD in the next ten years (39).
- a person with a high score (> 20) has greater than 20 percent risk of developing CVD in the next ten years (39).

This CVD risk estimate is seen as an important factor informing the intensity of approach to medication treatment (39).

OPPORTUNITY

Assess CVD risk in the population based on region specific data.

Whilst widely utilised, FRS was developed in the United States. As such, there is some concern that this clinical tool may not be generalisable across all ethnicities (41). With increased prevalence of disease risk factors, and genetic predisposition to conditions such as familiar hypercholesterolemia (FH) in KSA, consideration needs to be given to developing a region-specific CVD risk calculator. Stakeholders advised that regional country datasets from the past decade, could be accessed in the development of this critical clinical assessment tool.

How is CVD risk calculated?

A diagnostic test is any kind of medical test performed to aid in the diagnosis of a suspected disease or condition. This is different from a screening test which is used when asymptomatic people are considered to be at high risk of developing a disease (42). Apart from genetic predisposition, CVD is mostly preventable, provided that the risk factors are identified early using evidence-based screening tools (43).
To that end, a broad CVD screening program would identify the maximum number of patients requiring treatment.

The primary care setting is optimum for CVD risk screening, due to both relatively simple testing protocols and ease of access for most citizens.
In addition, rising costs and limited capacity across health systems, including hospitals, further support the primary care setting as the best option for any public health screening program (44).

In KSA, patients are able to self-select and attend a pathology lab for blood tests, without clinical referral. In order to support appropriate interpretation of results and allow clinical interventions, stakeholders noted that clinicians must receive these results and be supported to conduct follow-up care.

There is some precedence for screening programs in KSA. The Ministry of Health currently oversees two national screening programs in KSA (45). The first national screening program focuses on premarital screening for thalassemia, sickle cell disease, hepatitis B and C, as well as Human Immunodeficiency Virus (HIV) (45). The second national screening program focuses on newborn screening for metabolism and endocrine disorder inborn errors (46). Public awareness days for these screening programs are run annually (45).

What is cholesterol?

Atherosclerotic Cardiovascular Disease (ASCVD), within CVD, is characterised by the narrowing of arteries (atherosclerosis) resulting in restricted blood flow (2). ASCVD is caused by high levels of cholesterol, in particular 'bad' cholesterol, or low-density lipoprotein (LDL-C) (9).

Cholesterol is a fat-like substance, found in the blood stream and also in body organs and nerve fibres. It is necessary in the synthesis of some hormones and vitamin D as well as food metabolism (19 ,9). Cholesterol is transported through the bloodstream on two types of lipoproteins, these are (9):

- Low-density lipoprotein (LDL-C) makes up the majority of the body's cholesterol, also referred to as 'bad' cholesterol
- High-density lipoprotein (HDL-C) absorbs cholesterol and returns it to the liver, also referred to as 'good' cholesterol

In order to make informed clinical decisions, clinicians will seek a patient's lipid profile which includes LDL-C, HDL-C, as well as Triglycerides and Total Cholesterol (TC) (9).
A predominance of low HDL-C and high levels of LDL-C and triglycerides (TG), and high prevalence of co-morbid conditions such as diabetes, and hypertension further increase the risk of developing ASCVD (25 ,9).

Practice improvement incentives

A United States study in 2014 provided financial incentives across three primary care practices for three separate groups: physicians; physicians and patients; or patients only when the patient met their LDL-C goals (47). Patients were eligible if their 10-year FRS was greater than 20 percent and if they had significant coronary artery disease equivalent with LDL-C levels of 120 mg/dL or greater.

The primary outcome measure for this study was a change in LDL-C levels (47). A statistically significant reduction in LDL-C levels at 12 months was reported when financial incentives were shared between physicians and patients (47). This change was not observed when financial incentives were provided to physicians or patients only (47).

Data capture and transfer

Data collection and storage of results is essential in any screening program. A systematic digital interventions approach can close gaps in care for optimal LDL-C lowering for patients with established CVD (48). Successful implementation of big data solutions for CVD population health management requires a multidisciplinary approach, including data collection (quantitative and qualitative), digital storage and use, investment in big data platforms, harnessing technology to create novel digital applications, developing digital solutions that can inform the actions of clinical and policy decision makers and relevant stakeholders, and optimizing engagement strategies with the public and information-empowered patients (48).

Clinical decision support systems (CDSS) have been developed, implemented, and evaluated in diverse populations globally (48). The United States is implementing clinical and/or quality dashboards (49) to facilitate immediate access of information for clinicians thereby improving adherence to quality guidelines (50) and potentially improving patient outcomes (51). The Scripps Green Hospital in California developed and implemented a CDSS to improve heart team efficiency for transcatheter aortic valve implementation using an algorithm and rule- based alert system to integrate data and inform treatment decisions (52).

Similar tools have been implemented globally, including computerized decision support systems to manage CVD risk, and integrated with electronic medical records, as is the case in the Netherlands (53) (54). Another novel big data platform is Taltioni, a national data sharing platform in Finland with smartphone and mobile device applications that allow users to customize their health plans and access tools for blood pressure control, weight management and fitness, and medication schedule (55). These innovative data-sharing and patient-engagement platforms are increasingly being recognized as fundamental components of healthcare delivery, and as part of a nationwide public health response.

OPPORTUNITIES

01 Increase screening for CVD risk, including dyslipidaemia at the population level.

02 Incentivise family physicians to screen patients for CVD risk.

03 Enhance CVD risk assessment data capture and transfer.

04 Regular clinician follow-up of pathology results, including patient-initiated.

Reducing a major CVD risk factor - dyslipidemia

Research shows elevated cholesterol, or dyslipidaemia, is a significant risk factor for developing CVD globally and in KSA (8,13,15). Of the multiple other risk factors such as diabetes, smoking and hypertension, dyslipidaemia is easy to manage, with readily available cost-effective treatments. Modifying CVD risk by better management of dyslipidaemia is a simple and cost-effective means of addressing the burden of CVD in KSA.

While all risk factors and comorbidities must be considered holistically in the approach to managing the patients, personalised management to reduce the risk of future CVD events is required. Within this context, this report outlines actions the Governments in KSA can undertake to improve the management of elevated cholesterol, amongst the general population as well as those at risk of developing CVD.

This report outlines actions the Government in KSA can undertake to improve the management of elevated cholesterol.

Burden of disease

More than 30 percent of adults (18 years) in KSA are at high risk of CVD with an accompanying high prevalence of dyslipidaemia (35 percent) (57 ,56). A global cohort study in 2020 was conducted in 20 countries, including KSA where participants were randomly recruited from urban and rural communities from the Central province, Riyadh and Alkharj (33). As part of this Prospective Urban Rural Epidemiology (PURE) study there was an assessment of the demographic, behavioural and CVD risk factors of adults aged 70-35 years (33).
This study showed that 32.1 percent of participants had dyslipidaemia (33).

A prospective observational study in 2017 was conducted in 18 countries, including KSA and UAE (58). The DYSIS II study assessed lipid profiles, LDL-C levels and lipid lowering therapy (LLT) for patients with stable coronary heart disease (CHD) and in patients being hospitalized for an acute coronary syndrome (ACS) event (58). LDL-C target levels were assessed against the ESC/EAS guidelines. This study concluded that, on average, approximately 25 percent of study participants with very high CVD risk achieved the LDL-C target of <70 mg/dL (58).

Two related conditions

In addition to CVD resulting from a combination of lifestyle and other comorbidities, there are two conditions that, due to their high prevalence in KSA, warrant specific mention – Familial hypercholesterolaemia and metabolic syndrome:

01 Familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a genetic disorder which can result in high levels of cholesterol, in particular LDL-C (59). As indicated by the latest study at the multinational Gulf FH registry, the estimated prevalence for FH was 0.9 percent (1:112), showing higher prevalence in the Gulf region (3-fold the global prevalence) (7). It has been suggested that the prevalence of FH amongst Gulf countries is higher than the global population, in part due to the higher rate of consanguineous marriage i.e. first cousin marriages (59).

This higher rate of consanguineous marriage increases the risk of both Homozygous and Heterozygous familial hypercholesteremia (HoFH) which is associated with a high risk of early-onset fatal CVD outcomes (59). This is further compounded by delays in early and prompt diagnosis of any type of FH due to limited physician awareness.

A cross-sectional study in KSA in 2017 found that 93 percent of physicians across four Riyadh tertiary hospitals (273 of 294 total physicians surveyed) self-assessed as having poor FH knowledge (32).

There is a need to develop guidelines and increase awareness for clinicians around screening and cascade screening of family members to find patients with FH - **Family physician in KSA**

02 Metabolic syndrome

Metabolic syndrome comprises a combination of risk factors such as impaired glucose tolerance or diabetes, dyslipidaemia, hypertension, and obesity. These factors contribute to increased risk of CVD (60).

Metabolic syndrome in KSA affects almost 40 percent of the population, with a slightly higher rate amongst men as compared to women (34 percent compared to 29 percent) (61). Of concern is that 12 percent of young adults aged between 18 and 30 years in KSA have metabolic syndrome (62). For these young adults, low HDL is the most common component. Earlier diagnosis could also facilitate more targeted preventative interventions thereby reducing CVD risk in later life.

How do we reduce cholesterol and risk?

When considering options to treat elevated cholesterol, it is important to understand that lipid lowering treatments (LLT) reduce LDL-C or 'bad cholesterol' (15,63). The National Cholesterol Education Program (NCEP-III) advocates for physicians and healthcare specialists to initiate intensive reduction program in the levels of LDL-C for patients with CVD (56,57).

While LDL-C has been the primary biomarker for assessing dyslipidaemia, updated recent guidelines such as the ESC/EAS 2019 publication also include Lipoprotein (a) as a biomarker to be considered in assessing patients for inherited lipid disorders. (See box – Lipoprotein (a) and risk).

Lipoprotein (A) and CVD risk

Lipoprotein lipase (LpL) is an enzyme which is part of the lipase superfamily.
LpL is involved in the metabolism of all classes of lipoproteins, including the clearance of chylomicron remnants, formation of intermediate-density
lipoproteins (IDL) and low-density lipoproteins (LDL) from very-low-density lipoproteins (VLDL), and regulation of plasma high-density lipoprotein (HDL) concentrations (5,6).

Higher levels of plasma lipoprotein triglycerides are associated with increased risk of CVD (17). New treatments that enhance LpL activity are promising approaches to help treat hypertriglyceridemia and CVD (17). Enhancing LpL activity can lead to lower levels of Lipoprotein (a) which is known to carry atherosclerotic forming cholesterol.

Current options for treatment of high Lp(a) include the PCSK9 inhibitors. These PCSK9 inhibitors reduce Lp(a) levels by around 25-30 percent with or without combination statin therapy (22).

Enhancing clinician education

There is a current gap in how clinicians are measuring and managing dyslipidaemia. According to a cross-sectional study in KSA most physicians (94 percent) surveyed were familiar with metabolic syndrome but only 28 percent could correctly identify the serum LDL-C cut-off value for metabolic syndrome diagnosis (31).

Increased primary care physician awareness would support earlier diagnosis and effective management of dyslipidaemia for patients in KSA (31).

Stakeholders in KSA reported that capacity restraints in residency program results in up to 70 percent of graduates not receiving relevant training in chronic diseases, such as CVD.

Stakeholders also reported an opportunity to enhance clarity and utilisation of referral pathways for those patients failing to achieve target. It was suggested that family physicians could be supported by physician assistants, nurses, nurse practitioners and healthcare workers.

OPPORTUNITIES

01 Increase CVD training and education for practising physicians in the primary care setting.

02 Utilise a multidisciplinary workforce to support CVD risk assessment and patient care.

Best practice LDL-C management

Both ACC/AHA (United States) and ESC/EAS (European) 2019 guidelines for dyslipidaemia (3,22) are broadly used in KSA. Which guideline is followed depends on individual clinician preferences. These preferences may be on the basis of place of education, level of awareness, or other reasons.

Whilst both guidelines are broadly similar in approach (see Appendix C), there are some key differences in particular for the very high-risk population. These differences include:

- The European guidelines have adopted a lower LDL-C target for very high risk patients.
- LDL-C goals differ for very high-risk patients - <70mg/dL in United States guidelines and <55 mg/dL in European.
- with Ezetimibe or advanced therapies (PCSK9- inhibitors) in European than in the United States guidelines.

Regional guidelines

The evidence driving the ESC/EAS and ACC/ AHA international guidelines is based on data from Western countries. Research and stakeholders' interviews indicate that there are no local, consensus guidelines utilised in KSA. The development of guidelines suitable for the local population within Asian and Middle East countries has previously been proposed (35), along with development of regional guidelines for CVD management (8 ,39 ,64).

Given the high prevalence of dyslipidaemia, and CVD, in the region, as well as FH and metabolic syndrome, the development of a CVD region- specific guideline will provide a clear direction to the clinical community. This could also be translated into quality indicators which will work to support implementation and monitoring.

OPPORTUNITY Standard guidelines support a consistent approach to CVD risk and clinical care in KSA.

Treatment pathway

The following Figure 5 shows a high-level treatment pathway for dyslipidaemia in managing CVD (3 ,22).

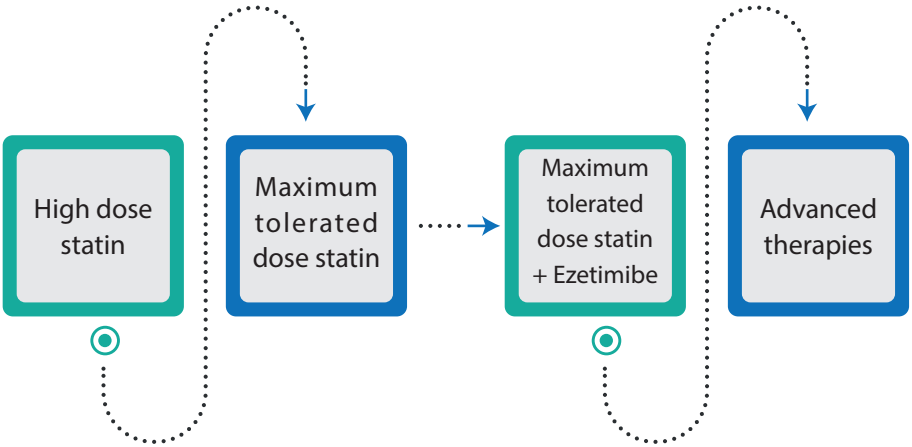


Figure 5 Flow chart for lipid management treatment pathway in KSA (3,22)

Lipid lowering treatment options

The risk of CVD events and mortality can be greatly reduced by LLT, which decrease the circulating concentrations of LDL-C (15). These therapies include statins, Ezetimibe, and other advanced therapies (15).

Statins:

Statins inhibit HMG-CoA reductase, the rate- limiting step in hepatic endogenous cholesterol synthesis (15,65). Statins are indicated in proven high-risk conditions, and treatment should be intensive to moderately intensive where the CVD risk is high to moderately high (35). Statins remain as first line treatment for dyslipidaemia.

Statins do not work for all patients. It has been suggested that there are some ethnicity-related differences in the LDL-C response to statins due to variation in the Proprotein convertase subtilisin/ kexin type 9 (PSCK9) gene (35,66,67). It is in these patients, that other therapies listed below become increasingly important.

> Statin adherence and health literacy is an issue.
> Patients stop taking the medication due to perceived side effects as it is not explained to them." **Family physician in Primary Health Care Unit**

Ezetimibe:

Ezetimibe inhibits the polytopic transmembrane protein, Niemann-Pick C1-Like 1 which is responsible for cholesterol absorption from the jejunal brush border (15,68). Ezetimibe has only recently become available in the formulary accessed by clinicians in KSA.

Advanced Therapies:

- Anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibodies inhibit PCSK9, a regulatory protein that binds to LDL-receptors on hepatocytes and promotes their routing into lysosomes for proteolytic destruction (,67 15). Access to PSCK9 inhibitors has only recently become available in KSA.
- Phase 1 and 2 trials have shown that synthetic small interfering ribonucleic acid (siRNA) treatments targeting PCSK9 lower LDL by up to 50 percent in patients at high or very high risk of CVD and patients with FH (69).

See Box – Lipoprotein (a) and risk, for further details on other modes of action for PCSK9 inhibitors.

OPPORTUNITY

Enhance patient awareness of CVD risk and the benefits of safe and effective treatment through public health campaigns.

Patients will only benefit if guidelines are being followed by both clinicians and patients. This includes adherence to the suitable diagnostic pathways, prescribing, and patient compliance with medical treatment (57). Stakeholders raised concerns that patient compliance was very low, and many examples were cited of low patient activation to commence or continue appropriate treatment. Public health approaches to care can only work if patient specific, barriers to uptake are considered. It is considered that a focused project to enhance both awareness of CVD and to support patient compliance is included in any public health approach.

Opportunities to reduce CVD burden

With a prevalence of CVD, and in particular, dyslipidaemia at over 30 percent, the KSA is at a critical juncture in how best to reduce the burden of disease.
Many of the patients at high-risk of death or a CVD related event, are young. The unfortunate tragedy of a premature death will not only deprive a family of a beloved member, but also KSA of a productive citizen who can contribute to the growth and prosperity of the nation.

Importantly, for most people, CVD is preventable and easily able to be treated. This report has identified how the KSA can leverage their health system to reduce CVD risk, death, and events.

Several areas of opportunity for policy makers in KSA were identified, these are:

- Assess CVD risk in the population based on region-specific data.
- Increase screening for CVD risk, including dyslipidaemia, at the population level.
- Incentivise family physicians to screen patients for risk.
- Enhance CVD risk assessment data capture and transfer.
- Facilitate clinical follow-up of pathology results, including patient-initiated.
- Increase CVD training and education for practising physicians in the primary care setting.
- Utilise the multidisciplinary workforce to support CVD risk assessment and patient care.
- Standardise guidelines to support consistent of approaches to CVD risk assessment and clinical care.
- Enhance patient awareness of CVD risk and the benefits of effective treatment.
- Ensure patient access to advances in clinical care and treatment.

There is an opportunity to improve cholesterol management for people in KSA. The following figure (Figure 6) shows the importance of a multifaceted population-based approach for management of dyslipidaemia. Only a comprehensive, multifaceted public health program will provide the opportunity to improve the management of dyslipidaemia and consequently reduce CVD risk in the KSA population.

Recommendations

This report presents a range of public health recommendations developed following a review of current literature, research, and interviews with key stakeholders in KSA. Input was sought from clinicians, cardiologists and family physicians, and health care policy makers.

Each of the recommendations work to significantly reduce elevated cholesterol and, as a result, the risk of CVD events in the current population, as well as reducing the associated burden of disease. Critically, by adopting a public health approach, the KSA Government will not only reduce the burden of disease, but drastically improve the health of future generations.

Our recommended approach includes consideration of all of the elements that influence clinical decision-making, as well as the lifestyle and behavioural approaches towards health living (70). Ultimately, the outcome of these recommendations is that each person in KSA is screened for their risk of CVD, the at-risk patients are monitored and treated to specific target cholesterol levels.

Our public health recommendations are:

01 | Develop a national CVD risk screening program with multiple access points in the community.

02 | Develop a region-specific CVD risk calculator.

03 | Develop region-specific CVD guidelines along with quality indicators to monitor implementation and impact.

04 | Develop a CVD digital dashboard to monitor risk, quality indicators and impact of guidelines.

05 | Develop a CVD course targeted at family health physicians.

06 | Enhance the role and education of other healthcare professionals in screening and monitoring of patients with CVD.

07 | Develop targeted public health awareness campaign that includes:
- The importance of screening for CVD risk.
- Patient education materials focused on treatment options and medication compliance.

The impact of a public health approach to CVD

To support the recommendations of this report, a discrete event economic model was developed, with evidence-based inputs. Further detail on the economic model can be found at Appendix A.

The recommendations have been quantitively assessed against the current burden of CVD in KSA and the results are stark.

Within the first five years of implementing a public health approach to CVD there will be:

112,748
fewer deaths

465,387
non-fatal CVD events avoided

The investment in healthcare to achieve this result is an additional SAR 11,269 (USD 3,005) per patient over the five years, this includes screening tests, healthcare professional costs and lipid-lowering therapies. This investment will lead to annual increase in productivity of SAR 1,905 million (USD 508 million) based on the number of deaths avoided (22,550 per year) and Gross Domestic Productivity per capita in 2018 of SAR 87,514 (USD 23,337) (30) This is likely a conservative estimate, as there will be an additional reduction in disability as a result of avoiding 465,387 non-fatal events, these people will also be able to participate in the growth and prosperity of the nation.

Additionally, the number of patients presenting with myocardial infarction (MI), stroke (both ischaemic and haemorrhagic) as well as revascularization procedures will decrease (Figure 7). Each of these events avoided represents a saving to the Government.

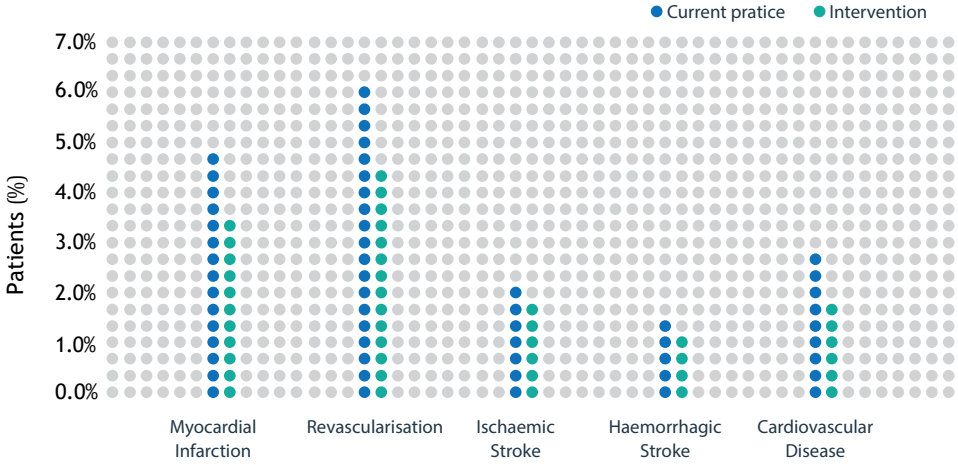


Figure 7 Impact of a public health approach

When the patients are modelled out over their lifetime, up to fifty years, the case for a public health approach to care becomes even more compelling:

1,439,340
fewer deaths

4,124,541
non-fatal CVD events avoided

Getting more patients to target

The first step in this public health approach is to identify the number of patients above the recommended target for dyslipidaemia, in particular LDL-C. Figure 8 below, reveals that, in the first five years, the number of patients at, or below the recommended targets increases dramatically. The patients below 77.3 mg/dL of LDL-C increases from less than 10 percent, to well over 60 percent, representing a more than eight-fold increase.

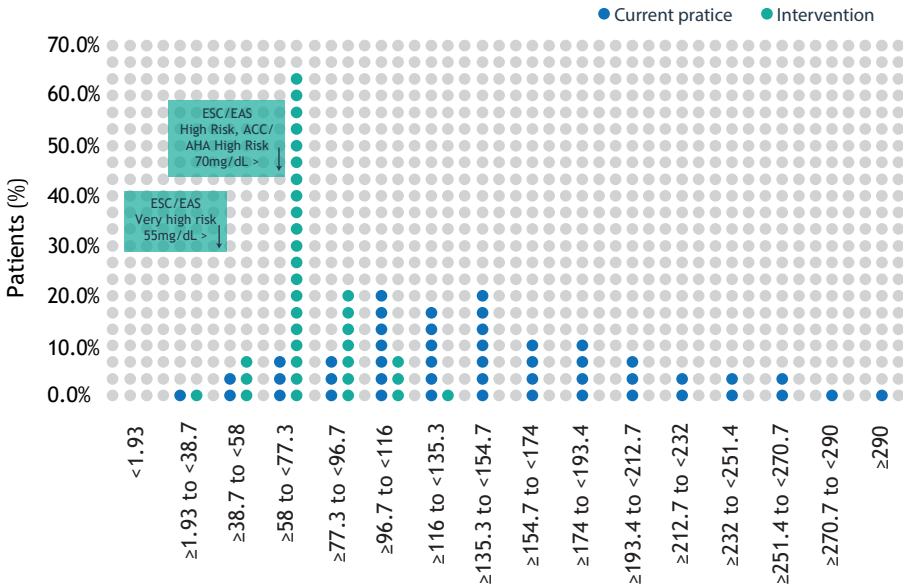


Figure 8 Change in LDL-C levels from a public health approach

Optimising therapy

The impact of optimising patients using the most appropriate therapy for their LDL-C level is highlighted in Figure 9 below. Our analysis reveals that there are currently around 70 per cent of at-risk patients on no treatment in KSA.

The recommendations in this report reduce this to less than 10 per cent of the cohort. Patients on combination and more advanced therapies also increases.

This optimal care is the primary driver of patients achieving a reduction in LDL-C.

Further, the testing and treatments utilised are individually cost-effective. This ensures that the public health approach presents value for money to Government.

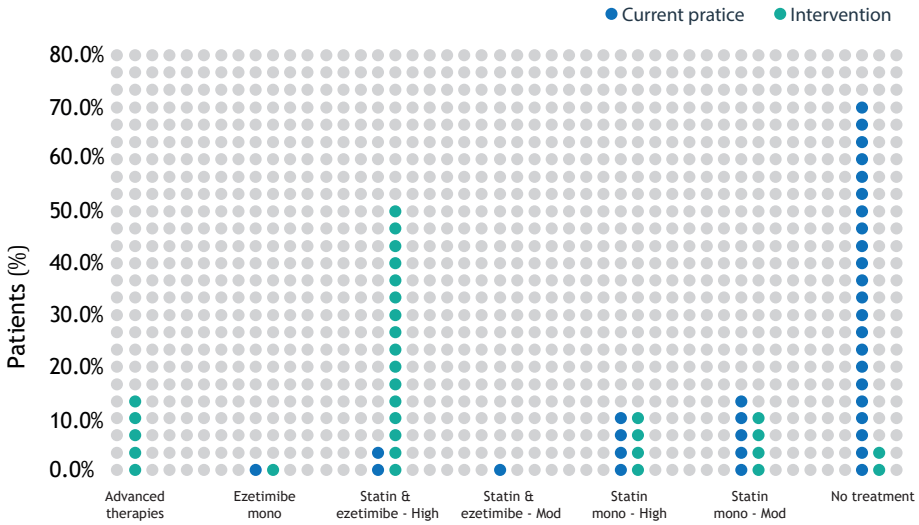


Figure 9 Optimising therapy with a public health approach (Economic modelling)

In conclusion, it can be seen that this multifaceted public health approach reduces the significant burden of CVD in KSA and provides a cost-effective method of improving the productivity of the nation.

Detailed Recommendations

01 Develop a national CVD risk screening program with multiple access points in the community.

With such a high prevalence of risk factors, comorbidities and CVD, the most efficient approach to identifying patients is through a population level screening program. CVD risk assessment protocol is easy to implement within the community, and as a result it is recommended that a range of access points are utilised – primary health centres, shopping malls, community centres and any other place where it is easy to access as many people as possible.

The screening program will utilise established cost-effective diagnostic testing protocols. Screening can be conducted by a range of healthcare professionals including medical doctors, nursing staff and allied health. In establishing this program, KSA could be amongst the first nation in the world to establish gold standard CVD screening and subsequent care. It is anticipated that most KSA citizens could be screened within the first five years of the program.

This screening program will need to be accompanied by a public awareness campaign (see recommendation seven).

02 Develop a region-specific CVD risk calculator.

Risk assessment needs to consider the specific characteristics of the KSA and Gulf region population, including concomitant risk factors and evidence of pre-disposition to a range of conditions, such as FH. To that end, it is recommended that a region-specific CVD risk calculator is developed. The development of this calculator, and associated clinical assessment tools, could utilise the extensive database of patient information from each country that is in scope.

This tool will need to be readily accessible by physicians, and other healthcare professionals, within their practice, as well as the national screening program (see recommendation one).

03 Develop region specific CVD guidelines along with quality indicators to monitor implementation and impact.

We recommend that the region consider developing a guideline for treatment of dyslipidaemia, that considers the higher prevalence of CVD risk and dyslipidaemia, in communication with the Saudi Heart Association (71) and National Heart centre KSA.

These guidelines will encourage a consistent approach to assessment and treatment of patients. Importantly, by recognising the very high- and high-risk patients, the guidelines may seek to encourage more intensive treatment to quickly reduce the risk in individuals and across the population.

To monitor the impact of a standard approach to care, we also recommend the development of accompanying quality indicators. These indicators will translate the key elements of the guidelines into best practice patient care for Government and clinical community.

04 Develop a CVD digital dashboard to monitor risk, quality improvement and impact of guidelines.

Building upon recommendation three, we propose the development of a CVD digital dashboard that tracks progress of the screening program and implementation of the risk calculator and guidelines. Maintained by the KSA Government, access to this dashboard should be granted to all those who work in primary care and public health.

Highly visual tools, such as dashboards, especially where targets are set, can motivate the clinical community to continue to seek out patients for risk assessment and initiation of therapy, where appropriate.

05 Develop a CVD course targeted at family health physicians.

One of the most effective ways of ensuring consistency of approach, is for the Government to develop and maintain an up-to-date CVD course targeted at family health physicians. As the primary point of health contact for the community, this training course will enhance the level of care offered to patients, and referral pathways to specialist care, cardiologists, or endocrinologists, are appropriately activated.

06 Enhance the role and education of other HCPs in screening and monitoring of patients with CVD.

With over 30 percent of the population at risk of a CVD event, resulting from dyslipidaemia; a higher prevalence of genetic disorders such as FH; and multiple other comorbidities such as metabolic syndrome – a population level screening program and new guidelines may stretch the current capacity of primary care physicians. It is therefore recommended that the role of other health care professionals, such as nurses, nurse practitioners and physician assistants is expanded so that they can participate in this critical program.

07 Develop targeted public health awareness campaigns that includes.

As discussed, in recommendation one, it will be critical for the Government to develop a targeted public awareness campaign to accompany the national screening program. Key messages could include:

- for most people, CVD is preventable.
- easy screening tests, can be done within 10-5 minutes.
- high prevalence of CVD in KSA.
- importance of annual testing of individuals, and their family members.
- ready access to safe and effective treatment, if appropriate.

In addition, to screening, we recommend the development of patient education materials focused on treatment options to support medication compliance.

Summary of recommendations and opportunities

This report identifies a range of opportunities that exist to improve the current approach to CVD in KSA. This summary table aligns these opportunities against the recommendations. (Table 1).

Recommendations

	Develop a national screening program with multiple access points in the community	Develop a region-specific CVD risk calculator.	Develop region specific guidelines along with quality indicators to monitor implementation and impact	Develop a digital dashboard to monitor risk, quality improvement and impact of guidelines
Assess CVD risk in the population based on region specific data	✓	✓	✓	✓
Increase screening for CVD risk, including dyslipidaemia, at the population level	✓	✓	✓	✓
Incentivise family physicians to screen patients for risk	✓	✓	✓	✓
Enhance CVD risk assessment data capture and transfer	✓	✓	✓	✓
Facilitate clinical follow-up of pathology results, including patient-initiated	✓		✓	✓
Increase CVD training and education for practising physicians in the primary care setting	✓	✓	✓	✓

	Develop a national screening program with multiple access points in the community	Develop a region-specific CVD risk calculator.	Develop region specific guidelines along with quality indicators to monitor implementation and impact	Develop a digital dashboard to monitor risk, quality improvement and impact of guidelines
Utilise the multidisciplinary workforce to support CVD risk assessment and patient care	✓	✓	✓	✓
Standardise guidelines to support consistent of approaches to CVD risk assessment and clinical care	✓	✓	✓	✓
Enhance patient awareness of CVD risk and the benefits of effective treatment	✓	✓		
Ensure patient access to advances in clinical care and treatment				✓

Table 1 Summary of recommendations and opportunities

	Develop a CVD course targeted at family health physicians	Enhance the role and education of other HCPs in screening and monitoring of patients with CVD	Develop targeted public health awareness campaigns
Assess CVD risk in the population based on region specific data	✓	✓	✓
Increase screening for CVD risk, including dyslipidaemia, at the population level	✓		✓

	Develop a CVD course targeted at family health physicians	Enhance the role and education of other HCPs in screening and monitoring of patients with CVD	Develop targeted public health awareness campaigns
Incentivise family physicians to screen patients for risk	✓		
Enhance CVD risk assessment data capture and transfer	✓	✓	✓
Facilitate clinical follow-up of pathology results, including patient-initiated	✓	✓	✓
Increase CVD training and education for practising physicians in the primary care setting	✓	✓	
Utilise the multidisciplinary workforce to support CVD risk assessment and patient care		✓	
Standardise guidelines to support consistent of approaches to CVD risk assessment and clinical care	✓	✓	
Enhance patient awareness of CVD risk and the benefits of effective treatment			✓
Ensure patient access to advances in clinical care and treatment	✓	✓	✓

Table 1 Summary of recommendations and opportunities

Appendix A Summary of economic model

An economic for KSA was developed to enable a quantitative assessment of the health costs and benefits of the recommended policy interventions by modelling the impact of improved lipid treatment adherence and escalation of the intensity of lipid.

The approach used to estimate CVD death, CVD non-fatal events and associated health system related costs was an economic evaluation based on a discrete event simulation (DES) model. The model is based on the CVD and CVD death, risk equations first developed by Anderson et al and published in 1991 and based on analysing data from the Framingham Heart Study (28,72). To ensure robust results that are relevant to a higher risk/secondary prevention population, the model was calibrated using data from the literature review (8,10,14,21,35,37,58,73).

An additional element of the model was to ensure that the baseline LDL-C levels and population characteristics of the model match those of the current population being considered in KSA in this report.

The model was populated with relevant indicators and cost data using published data in KSA (8 ,10 ,14 ,21 ,37 ,35 ,58,73), including cost of events such as myocardial infarction or Ischaemic stroke, pathology and medicine reimbursement costs and healthcare professional costs.

The baseline model used the LDL-C treatment (statin monotherapy, statin combination with ezetimibe, ezetimibe monotherapy, PCSK9 inhibitor) distributions from the published data in KSA (8,10,14,21,35,37,58,73).

Appendix B Database search strategy

A systematic data bases search strategy was conducted for published papers from 2021-2014 in English language in KSA and UAE. The EBSCOHOST databases included Academic Search Complete, CINAHL Complete, Global Health, Medline Complete, APA PsychInfo. The search strategy/MESH terminology included 'ldl' or 'low density lipoprotein' or 'cholesterol' or 'dyslipidaemia' AND 'saudi arabia' or 'kingdom of saudi arabia' or 'ksa' AND 'united arab emirates' or 'uae' or 'abu dhabi' or 'dubai'. The grey area literature search was conducted via GoogleScholar, and Science Direct.

Appendix C Summary of current guidelines

ESC/EAS 2019	ACC/AHA 2019
Very high risk: • ASCVD, clinical or unequivocal on imaging, • Diabetes with target organ damage or, • at least three major risk factors, • or early onset of type 1 diabetes of long duration of more than 20 years, • severe chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1.73 m2), • familial hypercholesterolemia with prior ASCVD or • another major risk factor or a 10-year risk estimate for CV mortality of at least 10 percent by the Systematic Coronary Risk Evaluation (SCORE) system **Target LDL:** Goal LDL-C level of <55 mg/dL or <1.4 mmol/L and at least 50 percent reduction from baseline LDL-C levels documented ASCVD diabetes with organ damage	**High risk (> 20 percent patient's risk of a CVD within the next 10 years)** Two or more prior ASCVD events One ASCVD event with multiple other high-risk conditions such as diabetes or severe hypercholesterolemia, defined as LDL of at least 190 mg/dL Measurement of coronary artery calcium measurement **Target LDL:** Goal LDL-C level of LDL-C level <70 mg/Dl or <1.8 mmol/L and at least 30 percent to 49 percent reduction from baseline LDL-C levels
High Risk Target LDL: Goal LDL-C level of <70 mg/dL or <1.4 mmol/L and at least 50 percent reduction from baseline LDL-C levels	**Intermediate risk (7.5 percent - 20 percent patient's risk of a CVD within the next 10 years)** **Target LDL:** Goal LDL-C level of <100 mg/dL (2.6 mmol/L) documented ASCVD diabetes with organ damage
Moderate risk Target LDL: Goal LDL-C level of <100 mg/dL	**Borderline risk (5 percent- 7.5 percent patient's risk of a CVD within the next 10 years)** **Target LDL:** Goal LDL-C level of LDL-C level <160 mg/dL (<4.1 mmol/L)
Low risk Target LDL: Goal LDL-C level of <115 mg/dL	**Low risk (<5 percent patient's risk of a CVD within the next 10 years)** **Target LDL:** Goal LDL-C level of 189- 70 mg/dL (4.9 - 1.8 mmol/L)

Table 2 Comparison of European and UNITED STATES guidelines

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