Atherosclerotic cardiovascular disease in Taiwan: a public health priority

September 2022

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About Evohealth

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Report at a glance

Tackling a leading cause of death: Atherosclerotic cardiovascular disease

Cardiovascular disease (CVD) is a leading cause of death and disability, accounting for almost one third of all deaths worldwide. Atherosclerotic cardiovascular disease (ASCVD) is a major contributor to the burden of CVD, accounting for an estimated 85 percent of cases globally. Yet when identified early, up to 90 percent of CVD deaths are preventable.

ASCVD is an important public health priority in Taiwan, with **40 percent people at risk** of developing this life-threatening disease.

A spotlight on hyperlipidemia

Hyperlipidemia is a serious condition arising from a build-up of LDL cholesterol in the arteries. It is a leading cause of ASCVD that elevates the risk of a heart attack, stroke or other cardiac event within five years. **Hyperlipidemia is Taiwan's fastest growing ASCVD risk factor**. The European Society of Cardiology identifies four modifiable risk factors for ASCVD – all of which are highly prevalent in Taiwan.

- **Hyperlipidemia** (high cholesterol) affects 44% to 58% of Taiwanese people.
- **Hypertension** (high blood pressure) affects 25% of Taiwanese people.
- Diabetes affects 10.3% of Taiwanese people.
- 13.1% of Taiwanese people are **regular smokers**.

Hyperlipidemia is easy to treat with readily available therapies. However, it is significantly undertreated in Taiwan. Many citizens do not recognise hyperlipidemia as a serious condition and there is low adherence to best practice treatments.

Saving lives and reducing burden of disease with a population health approach

A population health strategy works at scale to prevent the onset and worsening of ASCVD risk factors for all Taiwan citizens. This report sets out six population health recommendations to reduce the burden of ASCVD in Taiwan. These recommendations will lead to an estimated **19,115 lives saved** and **229,385 non-fatal CVD events avoided** in the first five years.

- 1. Develop a targeted **public health awareness campaign** that emphasises the importance of early detection and ongoing treatment of ASCVD risk factors.
- 2. Increase **screening of ASCVD risk factors** in young people to enable activation of primary prevention strategies, in line with clinical guidelines.
- 3. Develop a strategy for **continuous upskilling of primary care physicians on ASCVD** to improve compliance with clinical guidelines.
- 4. Develop a **framework for follow-up care** that empowers primary care physicians in the ongoing monitoring and management of patients with ASCVD
- 5. Partner with cardiac specialists and medical societies to develop **patient education** resources on ASCVD prevention and treatment.
- 6 **Expand patient access** to therapies in line with clinical guidelines and global best practice.

There is an opportunity for policy makers to commit to this multifaceted population health program to reduce the impact of CVD on the Taiwanese population and improve the health of the next generation.

Executive summary

Tackling a leading cause of death

Cardiovascular disease (CVD) is a leading cause of death and disability worldwide, accounting for almost **one third of deaths** (17.9 million) each year. While CVD is most common among those aged 65 years and older, it is increasingly occurring in younger people during the prime of their working and family lives.

Despite significant global investment in CVD awareness, prevention and screening, the prevalence of disease continues to rise. It is forecast that the number of CVD deaths globally will reach over **23 million by 2030**.

CVD is a preventable condition. Up to **90 percent** of cases can be prevented when risk factors are detected and treated early. With significant loss of life and growing pressure on already-strained healthcare systems, the imperative to reduce the global burden of CVD remains more important than ever.

When identified early, up to 90 percent of CVD deaths are preventable.

A spotlight on ASCVD

Atherosclerotic cardiovascular disease (ASCVD) is a major contributor to the burden of disease associated with CVD, accounting for **85 percent of cases.** ASCVD is a serious condition characterised by a build-up of cholesterol plaques in the arteries over time. This puts patients at elevated risk of a heart attack, stroke or CVD event.

ASCVD is a recognised public health concern in Taiwan. Ischemic heart disease (a condition arising from ASCVD) is a leading cause of death, with an estimated prevalence of **1.82 million** cases in Taiwan. Rates of ASCVD have risen steadily by **3.5 percent** since 2014, which is higher than other Asia-Pacific nations such as Japan (2.3 percent growth) and Australia (2.9 percent growth).

In Taiwan, the increasing prevalence of ASCVD has been underpinned by rising rates of cardiometabolic risk factors known as **'the three hypers'** – hyperlipidemia (high cholesterol), hypertension (high blood pressure) and hyperglycaemia (high blood sugar). The country's ageing population, sedentary lifestyles, adoption of high-fat western diets and rates of smoking all contribute to 'the three hypers'.

40 percent of adults in Taiwan have at least one of **'the three hypers'**, placing them at elevated risk of a heart attack or stroke.

It is estimated that **40 percent of Taiwanese people** have at least one of 'the three hypers', which significantly increases their likelihood of developing ASCVD. Among older Taiwanese people (65+ years), the prevalence of risk factors is even higher: **47.3 percent of older people have two or more** of 'the three hypers'. Achieving a meaningful reduction in the burden of ASCVD will require a paradigm shift from physician-centred care of individual patients to population-level interventions that prevent or delay the onset of ASCVD at scale. An evidence-based approach to reducing risk by targeting modifiable disease risk factors early can have substantial benefits in reducing CVD morbidity and mortality.

Four modifiable ASCVD risk factors

The European Society of Cardiology (ESC) identifies four risk factors for ASCVD – all of which have a high prevalence in Taiwan and most of which are modifiable:



Early detection and management of ASCVD risk factors reduces the lifetime risk of a heart attack, stroke or other CVD event. By taking action now, there is an opportunity to ease pressure on Taiwan's healthcare system, realise financial savings by reducing CVD events and, importantly, change the course of ASCVD for the next generation.

Changing the trajectory of ASCVD

There is an immense opportunity for a population health strategy that works at scale to reduce ASCVD risk factors for all Taiwan citizens. This white paper recommends a set of targeted population health policy solutions to reduce the burden of ASCVD. Many recommendations focus on **hyperlipidemia** – a known risk factor that often goes undetected, but once identified, is easy and cost-effective to treat.

Cholesterol complacency

is a key issue in Taiwan.

Hyperlipidemia is a common ASCVD risk factor in Taiwan, affecting between **43 and 58 percent** of adults. It has the fastest growth rate of all cardiometabolic risk factors, yet the lowest treatment initiation rate. **Up to 30 percent** of people do not consider hyperlipidemia to be a serious condition, which stands in contrast to hypertension and hyperglycaemia which are well-recognised health concerns.

A new approach to hyperlipidemia prevention and management is urgently needed.

Six population health recommendations

Our six population health recommendations are as follows:



These population-level recommendations can reduce the prevalence of ASCVD in Taiwan, as well as the number of fatal and life-threatening heart attacks, strokes and other CVD events. Critically, by taking a long-term view that addresses ASCVD prevention at scale, these recommendations can change the trajectory of CVD in Taiwan and improve the health of the next generation.

Quantifying the public health impact

We have quantified the health and financial impacts of the recommendations in this white paper using an economic model. By adopting the population health measures in this white paper, the anticipated impact is a significant reduction in deaths and disability due to ASCVD. Within the first five years, there will be **19,115 fewer deaths** and **229,385 non-fatal CVD events** avoided. Fewer CVD events results in fewer hospitalisations, reduced demand for chronic disease care and better quality of life for Taiwan citizens.





The investment in healthcare to achieve this result is an additional **NT\$32,031 (USD \$1,070) per patient over five years**. This includes screening tests, healthcare professional costs and lipid lowering therapies.

A multi-faceted population health approach to addressing hyperlipidemia is an affordable and impactful strategy for improving CVD outcomes in Taiwan. The population health approach to addressing ASCVD in Taiwan will result in:



Atherosclerotic cardiovascular disease in Taiwan: a public health priority

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Authors Renae Beardmore, Laura Birchall & Yukti Sharma.

Economic modelling Rudolf Schrover, Synevi.

Report design Naomi Guest.

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ASCVD – a global health priority

Cardiovascular disease – a global health priority

Cardiovascular disease (CVD) – a group of conditions that adversely affect the heart and blood vessels – is the leading cause of death and disability globally, with 17.9 million people dying from CVD in 2019 alone [3]. It accounts for a substantial burden of disease worldwide, with 31 percent of all deaths attributable to CVD [3].

Alarmingly, CVD is on the rise. The number of cases globally almost doubled from 271 million in 1990 to 523 million in 2019 [23]. The significant investments to date in disease awareness, prevention and screening have not been enough to stop the increasing prevalence of CVD around the world.

Tragically, the vast majority of CVD deaths are preventable, with up to 90 percent of cases arising from modifiable risk factors [24]. These include lifestyle factors (e.g. diet, smoking, exercise) and metabolic factors such as hypertension (high blood pressure), hyperlipidemia (high cholesterol) and hyperglycaemia (high blood sugar) [24].

The imperative to reduce the burden of CVD remains more important than ever.



What is CVD?

Cardiovascular disease (CVD) refers to a group of conditions that affect the heart and blood vessels.

Common conditions included within CVD are:

- Acute coronary syndrome
- Atherosclerotic cardiovascular disease
- Coronary heart disease
- Cerebrovascular disease
- Peripheral arterial disease

- Rheumatic heart disease
- Congenital heart disease
- Deep vein thrombosis
- Pulmonary embolism

CVD can lead to acute medical events such as heart attack (myocardial infarction), ischemic stroke and blood clots [3],[11].

The rising burden of atherosclerotic cardiovascular disease (ASCVD)

Atherosclerotic cardiovascular disease (ASCVD) is the most common form of CVD. It includes a range of conditions such as acute coronary syndrome, peripheral arterial disease, ischemic heart disease and ischemic stroke [25].

ASCVD is a preventable condition caused by high levels of low-density lipoprotein cholesterol (LDL-C), known as 'bad cholesterol' [6]. A build-up of LDL-C over time leads to narrowed arteries (atherosclerosis) and restricted blood flow from the heart.

An estimated 300 million people worldwide live with ASCVD, facing each day with an elevated risk of a life-threatening or life-limiting myocardial infarction (heart attack), ischemic stroke or other CVD event [23].

The growing burden of ASCVD in Taiwan

ASCVD is an important public health issue in Taiwan, with an estimated 1.82 million cases (accounting for 79 percent of all CVD cases) [19]. The prevalence of ASCVD has risen by 2.3 percent annually since 2014 [19], underpinned by rising rates of 'the three hypers' – hyperlipidemia, hypertension and hyperglycaemia [19]. It is estimated that, in combination with obesity, these cardiometabolic risk factors accounted for as many as 12,120 CVD-related deaths in Taiwan in one year alone [26].

The increasing prevalence of ASCVD in Taiwan can be attributed to a range of population, demographic, socioeconomic and lifestyle factors:

Ageing population:

Taiwan has one of the world's fastest ageing societies, with a rate of population ageing (e.g. growth in the proportion of people older than 65) more than twice that of the United States or Europe [27]. It will become a 'super-aged' society by 2026, with one in five people aged 65 years and older [19]. With 61 percent of ASCVD cases occurring in this age group, the burden of ASCVD is forecast to increase substantially in line with population ageing [19]. "Our population is ageing very fast. There will be many more people with comorbidities, risk factors and cardiovascular disease." - Clinician in Taiwan "We need to move, move, move! There is less time for movement in people's lives now, they are busy with work and their families. Food delivery services mean it's often easiest to eat takeout." - Cardiologist in Taiwan

Lifestyle factors:

The combination of sedentary lifestyles, smoking and the adoption of western diets that are high in calories, fatty acids, sodium and oil has had an observable impact on population health in Taiwan. As a result, more Taiwan citizens are at risk of developing ASCVD [28],[14].

Cardiometabolic and genetic factors:

Cardiometabolic and genetic conditions are common in Taiwan. Hyperlipidemia, hypertension and hyperglycaemia are on the rise and increase in prevalence with age [28],[19]. The genetic condition familial hypercholesterolemia (FH) also occurs frequently, with a detection rate of 3.8 percent (approximately 100,000 patients) [7],[14]. This is comparable to western countries and somewhat higher than other Asian countries (e.g. Hong Kong, Malaysia, Japan and China) [7]. "Hypertension, diabetes, lipid control – these are major challenges in Taiwan and need to be controlled aggressively."

- Clinician in Taiwan

What is Familial Hypercholesterolemia?

Familial Hypercholesterolemia (FH) is a common lipid disorder affecting 1 in 200-500 people globally. It is caused by gene mutations and results in lifelong high cholesterol (elevated LDL-C) and atherosclerosis [2],[7].

FH increases the risk of CVD by up to 20-fold in untreated patients and 10-fold in patients taking statins [14]. This highlights the urgency of early detection and effective treatment. Once identified, FH is easy to treat with lipid lowering therapies. It can rarely be treawted with dietary, exercise and lifestyle modifications alone – these only achieve a 10-15 percent reduction in LDL-C levels [17]. Due to the modest effect of statins in FH patients, novel treatment options (e.g. mipomersen, lomitapide, PCSK9 inhibitors) are needed to reduce LDL-C levels to acceptable ranges [14].

FH is a chronically undertreated condition, with up to 62.5 percent of patients undiagnosed or underdiagnosed [2]. Awareness and knowledge of FH is low in Asia (including Taiwan), with only 34 percent of physicians reporting that they were familiar with the condition [2].

Taiwan is taking measures to improve detection and management of FH, with the detection rate increasing from less than 1 percent in 2013 to 3.8 percent in 2019 [7]. More than 1000 patients have been enrolled in the Taiwan FH Registry supported by the Taiwan Society of Lipids and Atherosclerosis for active management.

Four key risk factors for ASCVD

The European Society of Cardiology (ESC) identifies four key risk factors for ASCVD – hyperlipidemia, hypertension, diabetes and smoking – all of which are highly prevalent in Taiwan (Figure 1) [29]. It is estimated that over 40 percent of Taiwanese adults have at least one of 'the three hypers' [10] and almost 50 percent of older people (65+ years) have two or more of these conditions [4].



Figure 1. Four risk factors for ASCVD

It is important to note that, although ASCVD risk factors are primarily concentrated among older people, younger Taiwanese people are not immune from developing cardiometabolic conditions that lead to ASCVD. There was a 30 percent increase in the number of young people (<55 years) in Taiwan who experienced a heart attack (acute myocardial infarction) between 2009 and 2015 [22]. This underscores the importance of prevention and early detection of ASCVD.

Heart attacks in young people (<55 years) in Taiwan increased by **30 percent between 2009 and 2015**.

Taiwan National Plan for the Prevention and Treatment of CVD (2018-22)

ASCVD is recognised as an important health priority in Taiwan, both by the central government and key medical societies. At a government level, there is a focus on preventing and controlling 'the three hypers': hyperlipidemia, hypertension and hyperglycaemia [1].

The National Plan for the Prevention and Treatment of CVD (2018-22) sets control rates for the 'three hypers', both for the general population and high-risk groups [4]. It includes measures to address the burden of disease associated with CVD and reduce premature deaths by 25 percent. These measures include healthy lifestyle education, early detection of risk factors, enhanced data collection and interventional studies on hyperlipidemia, hypertension and hyperglycaemia, among other measures [4],[15].

A population health approach to addressing ASCVD

The evidence is unequivocal that ASCVD is a critical public health concern, both in Taiwan and on a global scale. Without further action, the burden of disease will continue to rise for patients, their families and the healthcare system.

A framework for ASCVD prevention

Management of ASCVD has traditionally focused on physician-centred care that addresses risk factors with individual patients. While this remains important, greater impact can be achieved with complementary investment in preventive health strategies that operate at a whole-of-population scale.

A population health approach to ASCVD focuses on the prevention and treatment of risk factors before they progress to clinically significant or worsening disease. It also delivers interventions that improve health outcomes at scale, benefiting whole populations or cohorts rather than individual patients. Disease prevention is a cornerstone of a population health approach. Through this lens, there are three areas of focus (Figure 2):

- **Primary prevention** aims to prevent the onset of disease and disease risk factors by encouraging healthy behaviours in all members of a population.
- Secondary prevention aims to prevent patients with ASCVD or established risk factors from experiencing a CVD event.
- **Tertiary prevention** aims to improve quality of life after an ASCVD event.

Primary pre	evention	Secondary	prevention	Te	ertiary pre	vention	
Interventions targeted at healthy people to maintain health before disease occurs (e.g. nutrition, exercise) Early detection of disease (e.g. screening) before signs or symptoms arise to prevent onset or progression of illness		tion of g. screening) s or arise to set or n of illness	Tr sy to se qu ca	reatment of reduce d everity and uality of lif ardiac reha	of ic patients isease I improve e (e.g. abilitation)	•	
Policy or regulatory change	Behavioural change	Early detection	Risk factor reduction	Ac mar	cute case nagement	Rehabilitation & ongoing management	



Primary prevention of ASCVD

The term 'primary prevention' refers to measures that target all members of a population to prevent the development of disease risk factors and, in turn, delay or stop the onset of clinically significant disease. It typically focuses on the promotion of healthy lifestyle behaviours (e.g. exercise and diet), as well as the use of preventive therapies (e.g. medication to lower hypertension or hyperlipidemia).

Preventive health checks in Taiwan

A valued health initiative in Taiwan is the adult health check, funded by the Health Promotion Administration. Adults aged 40-64 can access preventive healthcare services once every three years for assessment of general risk factors (e.g. blood pressure, waist circumference, lipid levels, smoking, diet, exercise, alcohol) and to enable early intervention (19) (20).

There is evidence to support the value of primary prevention for ASCVD. For example, the seminal INTERHEART study (with a sample of 27.000 people from 52 countries) found that 90 percent of heart attacks (acute myocardial infarction) were attributable to nine modifiable risk factors: hyperlipidemia, hypertension, hyperglycaemia, smoking, obesity, psychosocial factors, diet, exercise and alcohol [35]. A population health strategy that identifies and addresses modifiable risk factors early, before they lead to the onset of ASCVD, can substantially reduce the burden of disease.

Figure 3 reiterates the importance of a population health approach as part of primary prevention [36]. It shows that a population health strategy that addresses risk factors early can reduce the number of patients at high risk of a CVD event.



Figure 3. Impact of a population health strategy [36]

Secondary prevention of ASCVD

The term 'secondary prevention' refers to measures that aim to prevent CVD events (such as acute myocardial infarction, ischemic stroke, blood clots and other events) in patients with established ASCVD risk factors or clinically significant disease. It is a critical pillar of any population health approach, as these patients are at greatest risk of experiencing a life-threatening or life-changing CVD event.

Common secondary prevention strategies include health screening, risk assessment and risk reduction. Medications that work to reduce LDL-C levels and hypertension are frequently used risk reduction strategies for secondary prevention of ASCVD.

In secondary prevention of ASCVD, patients are stratified into risk categories (typically ranging from low or minimal risk to very high risk) based on factors such as age, sex, cardiometabolic risk factors and LDL-C levels. This is used to guide the intensity of therapeutic interventions. Across all risk cohorts, the goal of secondary prevention is to reduce LDL-C levels (and other relevant risk factors) to reduce the risk of a CVD event and premature death.

Assessing ASCVD risk in Taiwan

Risk assessment is an important determinant of the appropriate treatment pathway for patients with ASCVD or established risk factors. Many risk calculators are in use globally:

- Framingham Risk Score (FRS)
- Pooled cohort equation (American College of Cardiology & American Heart Association)
- SCORE (European Society of Cardiology and European Atherosclerosis Society)
- QRISK2 (UK National Institute for Health and Care Excellence)

However, none of these models have been validated in East Asian populations. Taiwan has therefore chosen to use a point-based prediction model that uses data from a national cohort study in the 1990s. This model considers patient age, sex, body mass index, systolic blood pressure, smoking and lipid levels (total cholesterol, LDL-C and HDL-C) [8].

The level of ASCVD risk is determined by the number of risk factors that apply to a patient (e.g. a patient with one risk factor is at low risk, whereas two or more risk factors are considered moderate risk) [16]. Although imperfect, Taiwan's CVD risk assessment model enables a convenient approach to risk stratification for informing treatment decisions [16].

Tertiary prevention of ASCVD

The term 'tertiary prevention' refers to measures that improve quality of life in ASCVD patients who have experienced an acute myocardial infarction, ischemic stroke or other CVD event through symptom management and rehabilitation. In line with global best practice, cardiac rehabilitation (CR) is recommended as a tertiary prevention strategy to improve health outcomes and quality of life for ASCVD patients [37].

Effective CR programs support patients through exercise, lifestyle education, disease management and psychosocial support. CR focuses not only on the CVD event and its impacts, but also seeks to address comorbid and contributing conditions [37]. There are numerous benefits of CR. It has been shown to reduce hospital admissions by up to 18 percent, reduce mortality by up to 47 percent and improve medication adherence by up to 65 percent [37],[38]. CR therefore improves patient health outcomes and reduces pressure on the healthcare system.

It is estimated that Taiwan has 35 CR programs to support its high volume of eligible patients, with lack of patient referrals and lack of human resources being key barriers to expanding services [39]. The utilisation rate of CR programs is 46 percent [40], which represents an opportunity to improve patient access.



Increase the availability and encourage the uptake of cardiac rehabilitation for all people who have experienced a CVD event.

Targeting a major ASCVD risk factor – hyperlipidemia

Hyperlipidemia is a major risk factor for ASCVD. High levels of LDL-C cause fatty plaques to build up in the arteries over time, leading to the onset of ASCVD. This puts patients at an elevated risk of an acute myocardial infarction, ischemic stroke or other life-threatening CVD event within five years [6],[28].

What is cholesterol?

Cholesterol is a fat-like substance found in the blood stream, organs and nerve fibres. It is needed for the synthesis of some hormones and vitamin D, as well as food metabolism [5, 6].

Cholesterol is transported through the bloodstream on two types of lipoproteins:

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

The risk of ASCVD increases with high levels of LDL-C and triglycerides, or low levels of HDL-C [6, 12]. To make informed clinical decisions, clinicians need to understand a patient's full lipid profile which includes LDL-C, HDL-C, triglyceride levels and total cholesterol levels [6].

In Taiwan, the term 'hyperlipidemia' is used for a range of conditions associated with high cholesterol. This includes high levels of LDL cholesterol ('bad cholesterol'), low levels of HDL cholesterol ('good cholesterol') and high levels of total cholesterol and/or triglycerides [17].

Hyperlipidemia on the rise

Worryingly, hyperlipidemia is on the rise in Taiwan at a rate of increase that outpaces other CVD risk factors. Hyperlipidemia is growing at a rate of 3.2 percent, compared to 1.6 percent for hypertension and -0.9 percent for diabetes [19]. The good news is that, compared to other ASCVD risk factors, hyperlipidemia is easy to treat with readily available and affordable therapies. Population health strategies that target hyperlipidemia therefore represent a simple and cost-effective means of reducing the burden of CVD.

Best practice in LDL-C management

There are extensive research findings and clinical guidelines on effective treatment of hyperlipidemia. Healthy lifestyle choices such as dietary change, physical activity, smoking cessation and low alcohol intake are undoubtedly beneficial for patients with elevated LDL-C [16]. However, lifestyle modification alone is rarely sufficient for people with hyperlipidemia to reach desired LDL-C levels [11]. Evidence shows that lifestyle modifications result in only a 10 to 15 percent reduction in LDL-C levels [17]. For most patients, this is inadequate to address their risk exposure to a CVD event.

Lifestyle modifications generally result in only a **10-15 percent** reduction in LDL-C levels [17].

Lipid lowering therapies

Lipid lowering therapies are shown to be clinically effective in reducing LDL-C levels.

The goal of lipid lowering therapy is to achieve and maintain optimal LDL-C levels. While targets vary by a patient's risk level and the clinical guideline being applied, targets of <55-70 mg/ dL are usually set for very high risk patients, while <100 mg/dL is generally accepted for lower risk groups [41]. Lifelong treatment with lipid lowering therapy is required to sustain lowered LDL-C levels over time. International guidelines from the American College of Cardiology (ACC) / American Heart Association (AHA) and the European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) recommend lipid lowering therapies in conjunction with healthy lifestyle behaviours for primary and secondary prevention of ASCVD [42],[18]. Statin therapy is universally recommended for high risk patients [42],[41].

The lower the LDL-C level, **the lower a patient's absolute risk** of experiencing a CVD event.

Lipid management in Taiwan

Clinical guidelines

Taiwan has taken measures to address the rising burden of ASCVD by improving lipid control. The 2017 Taiwan Lipid Guidelines (TLGs) were developed as a population-specific methodology to better meet the needs of high risk ASCVD patients. The TLGs were a response to the worsening burden of ASCVD in Taiwan, indicated by a rising mortality rate, low prescribing rates for lipid lowering therapies and poor control rates of hyperlipidemia [41].

The TLGs broadly align with the ESC/EAS (European) guidelines, although there are some differences due to epidemiological differences:

- There are differences in the definition of ASCVD and classification of high risk patients. For example, intracranial arterial stenosis (which occurs more often in Asians than Caucasians) is included as a high risk condition in the TLGs.
- Additionally, the TLGs historically set a higher treatment target (<100 mg/dL) for ischemic stroke patients, although this has been revised to align with ESC/EAS guidelines in the 2022 update [16]. The higher treatment target for ischemic stroke patients reflected concerns about a risk of haemorrhagic stroke associated with intensive LDL-C lowering in Chinese people. However, a subsequent meta-analysis of 31 randomised controlled trials has since demonstrated no association between statin use and haemorrhagic stroke [41].

The TLGs are underpinned by a target-driven methodology to reduce LDL-C levels. A target-driven methodology means that a moderate or high-intensity statin is initially prescribed to patients, with progressively higher doses then prescribed as needed to achieve desired LDL-C targets [41]. "The TLGs are very suitable for our patients, we just need all clinicians to follow them step-by-step. We need to conquer clinical inertia and treat patients according to the guidelines." - **Clinician in Taiwan**

Availability of lipid lowering therapies

Several lipid lowering medications are subsidised by National Health Insurance (NHI) in Taiwan, making them accessible and affordable for patients. These therapies are supplied in an established treatment escalation pathway that commences with the maximum-tolerated dose of statins and progresses to combination therapy with ezetimibe if needed. In some cases, patients may receive a PCSKg inhibitor.

- **Statins** are the first-line treatment for hyperlipidemia that work by reducing the amount of cholesterol in the liver and bloodstream to reduce the risk of heart disease, acute myocardial infarction and ischemic stroke. Statins must be taken longterm for sustained LDL-C reductions and are generally well tolerated [20].
- **Ezetimibe** is used in combination with a statin for patients who are unable to reach

their LDL-C target with statins alone, or those intolerant to statins. It works by reducing cholesterol absorption and is therefore often prescribed alongside a low cholesterol diet [14].

 Advanced therapies are lipid lowering medications such as PCSK9 inhibitors that reduce concentrations of lipoprotein (a), which carries atherosclerotic forming cholesterol. They are highly effective and have been shown to outperform statins, with clinical trials demonstrating reductions in LDL-C levels of up to 50 percent in high risk patients [43]. However, due to their high cost, the NHI sets strict limits on their usage. This makes them harder to access in Taiwan than recommended under ESC/EAS guidelines (Figure 4) [14],[44].

	Eligible population for PCSK9	Treatment approach
2020 Taiwan NHI regulation	Patients who have experienced a major ASCVD event within 1 year including myocardial infarction, coronary artery disease, peripheral arterial disease, other arterial disease that received vascularisation or atherosclerosis-related ischemic stroke. Ezetimibe must have been used before prescribing PCSKg.	Threshold approach for all LDL-C >135 mg/dL
2019 ESC/EAS guideline	Patients with clinically established ASCVD or recurrent vascular events within two years whilst on the maximally tolerated statin. It is optional by clinical judgement to use Ezetimibe before prescribing PCSK9.	Target approach of LDL-C <55 mg/dL for ASCVD and <40 mg/dL for patients with recurrent vascular events

Figure 4. Taiwan NHI regulations and ESC/EAS guidelines for PCSK9 inhibitors [44]



Lipoprotein (a) and CVD risk

While LDL-C has been the primary biomarker for assessing hyperlipidemia, there is a growing focus on the role of Lipoprotein (a) as a biomarker for inherited lipid disorders. Lipoprotein lipase (LpL) is an enzyme in the lipase superfamily. LpL is involved in metabolism of all classes of lipoproteins, including clearance of chylomicron remnants, formation of intermediate-density lipoproteins and low-density lipoproteins (LDL) from very-low-density lipoproteins (VLDL), and regulation of plasma high-density lipoprotein (HDL) concentrations [9, 10].

New treatments that enhance LpL activity are promising approaches to help treat hypertriglyceridemia and CVD [13]. Enhancing LpL activity can lead to lower levels of Lipoprotein (a) which is known to carry atherosclerotic forming cholesterol. For example, PCSK9 inhibitors are used to treat high Lp(a). PCSK9 inhibitors reduce Lp(a) levels by around 25-30 percent with or without combination statin therapy [18]. Lp(a) measurement at least once in all adults is recommended by the ESC/EAS [18].

Primary prevention of hyperlipidemia

There is growing evidence to intervene early and control LDL-C aggressively

In 2022, the Taiwan Society of Lipids and Atherosclerosis (in partnership with seven other societies) published the 2022 Taiwan Lipid Guidelines for Primary Prevention, which sets out LDL-C targets and treatment strategies for people who have not yet developed clinically significant ASCVD. The guidelines recommend immediate initiation of statin therapy, in parallel with lifestyle change, for high risk patients with diabetes, chronic kidney disease, FH or LDL-C levels >190 mg/dL. In moderate and low risk patients with ASCVD risk factors, statins are recommended after three months of lifestyle changes (Figure 5).

In Taiwan, patients are required to undergo three to six months of lifestyle changes before they can receive subsidised access to lipid lowering therapies [19, 20]



Figure 5. Recommended treatment pathway for primary prevention of ASCVD [16]

Secondary prevention of hyperlipidemia

The 2017 and 2022 TLGs set out treatment pathways and LDL-C targets for patients with ASCVD (coronary artery disease, acute coronary syndrome, ischemic stroke and peripheral arterial disease) or key risk factors (diabetes mellitus, chronic kidney disease and FH) [16] (Figure 6).



*Ischemic stroke/TIA with cerebral or carotid atherosclerotic stenosis or known CAD

Figure 6. Recommended treatment pathway for secondary prevention of ASCVD [16]

The evidence shows that lifestyle modifications only result in a 10 to 15 percent reduction in LDL-C levels [17]. Yet under NHI guidelines, ASCVD patients must undergo three to six months of lifestyle modification prior to commencing lipid lowering therapy [19, 20]. This is a barrier to timely access to effective treatments.

Review NHI reimbursement requirements to enable access to lipid lowering therapies as early as possible, in parallel with lifestyle changes.

Key barriers to addressing hyperlipidemia in Taiwan

While a range of treatments are readily available to treat hyperlipidemia, there are several barriers that must be overcome to reduce its prevalence and the associated burden of disease in Taiwan.



Policy barriers

Hyperlipidemia is not prioritised as a risk factor

While there is good awareness of hypertension, diabetes and obesity as modifiable risk factors for CVD in Taiwan, the same profile has not been given to hyperlipidemia. For example a recent survey indicated that approximately 30 percent of people in Taiwan did not consider hyperlipidemia to be a serious condition [19].

"There is a lot of inertia about hyperlipidemia as a risk factor, both from patients and physicians." - Cardiologist in Taiwan

OPPORTUNITY

Deliver a targeted public health campaign to educate people about the serious health risks associated with hyperlipidemia.

Limited patient access to advanced therapies

Taiwan provides universal health coverage for its citizens, with reimbursement of essential medications to ensure affordability and accessibility for patients. Under NHI arrangements, statins have been reimbursed for ASCVD patients since 1995 [20].

However, there are some gaps between best practice clinical recommendations and insurance

coverage decisions. For example, access to high-cost advanced therapies is restricted to patients with FH, very high risk patients and those who do not respond successfully to statins or combination therapy [44]. Strict reimbursement criteria can mean that patients who may otherwise benefit face high out-of-pocket costs to access highly effective therapies [19].

OPPORTUNITY -

Conduct a cost-effectiveness analysis to inform future decisions about NHI coverage of advanced therapies.



Population barriers

Hyperlipidemia is a silent symptom

Unlike hypertension or hyperglycaemia, which are often accompanied by pain or discomfort, patients with hyperlipidemia can be asymptomatic. Until the condition reaches severe stages, patients do not feel unwell because of elevated LDL-C levels, and similarly, do not feel noticeably better when their LDL-C levels decrease [45].

Due to the silent nature of hyperlipidemia, many undiagnosed patients do not realise they are living with a condition that can lead to ASCVD and therefore have no reason to seek treatment [46]. Underdiagnosis of hyperlipidemia is a challenge for Taiwan, with less than 50 percent of cases detected in young people (below 55 years) [19]. "Most patients care about their blood pressure and sugars. They don't care too much about their cholesterol because there are no signs or symptoms. They don't have a sensation that it might be a problem."

- Cardiologist in Taiwan



OPPORTUNITY 🔶

Increase screening opportunities to detect silent cases of hyperlipidemia, such as in routine primary care visits or workplace health promotion programs.

There are low rates of prescribing for lipid lowering therapies

"Education of the medical community is very important – not just cardiac specialists, but nurses and broader care teams too. We need a structured program for effective education for all clinicians."

- Clinician in Taiwan

Patients in Taiwan are less likely to be prescribed effective lipid lowering treatments than in other countries. In general, fewer ASCVD patients in Asia are prescribed statins and fewer patients reach LDL-C targets than their European counterparts [21].

In Taiwan, only 70 percent of ASCVD patients are prescribed lipid lowering medications on discharge from hospital [21], thus representing a missed opportunity for an evidence-based clinical intervention.

Low prescribing rates are thought to reflect physician reluctance, expectations of patient reluctance and concern about side effects [19]. Despite evidence that statins are generally safe and well tolerated, up to 30 percent of healthcare providers in Taiwan report concerns about side effects and drug reactions [19]. This signals an important need for clinician education [19].

OPPORTUNITY 🕂

Provide regular training to all clinicians working with ASCVD patients to ensure awareness of the latest evidence and guidelines in relation to treatment options.

Many patients do not adhere to treatment regimens

1 in 3 ASCVD patients in Taiwan stop taking their prescribed medications within one year [20]

Rates of medication compliance are poor among ASCVD patients in Taiwan. Only 41 percent of ASCVD patients adhere to prescribed medicines in accordance with their physician's instructions, and fewer than 50 percent continue to take their medicines after two years (despite hyperlipidemia requiring lifelong treatment) [19],[20].

The risks of discontinuing treatment are significant. Poor medication adherence in ASCVD patients accounts for an estimated 10 percent of

hospital admissions and contributes to 125,000 deaths per year in the United States alone [20].

Poor treatment compliance in Taiwan is thought to reflect low perceived benefits of treatment, concerns about side effects and confusion about the need for long-term adherence. Many patients hold the misconception that medication can be stopped once an initial lowering of LDL-C levels has been reached [19],[46].

"Patients usually do well on their medication for 6 months, but then they start to worry about myalgia, liver function and other symptoms. They might stop taking their statin or reduce their dose... and patients are usually reluctant to tell us when they haven't been compliant."

- Cardiologist in Taiwan

"Once patients reach their LDL-C target, many believe they are cured and there is no need to continue taking medications or making lifestyle changes." - Clinician in Taiwan

Control rates of hyperlipidemia are suboptimal

Control rates of hyperlipidemia are well below target rates in Taiwan. Fewer than 54 percent of ASCVD patients reach the desired LDL-C target of <100 mg/dL, and so remain at high risk of a CVD event [21]. This is concerning because ASCVD patients have a high risk of recurrent CVD events. Failure to achieve target LDL-C levels elevates their risk, exposing patients to a possible CVD event sooner.

Misconceptions about lipid lowering therapies

There are a range of misconceptions about lipid lowering therapies held by patients and physicians alike that impact on prescribing rates and medication compliance:

- The role of diet and exercise: A recent survey indicated that 70 percent of people in Taiwan believed that diet and exercise alone are sufficient to manage hyperlipidemia [19]. This is consistent with clinician observations of a general preference among patients for natural therapies over medicines. However, this runs counter to empirical evidence and clinical guidelines showing that lifestyle change is necessary, but not sufficient, to reduce risk associated with ASCVD [17].
- Concern about side effects: There are concerns about side effects, adverse effects and poor tolerance of statins in Asian populations, particularly muscular and hepatic side effects [47], [48]. While statin intolerance occurs in a reported 10 to 25 percent of statin users in Taiwan, these numbers are controversial due to challenges in proving causality between statins and symptoms [48]. When statin intolerance does arise, there are effective strategies to manage it in Taiwan [48].

"There are serious problems with misinformation about the side effects of statins in Taiwan. 90 percent of my patients can take statins with no issues, and we can change the settings to help the 10 percent who might experience side effects." - **Clinician in Taiwan**

Misconceptions about lipid lowering therapies

• **Concern about haemorrhagic stroke:** There are residual concerns among patients and some clinicians about statin usage as a risk factor for haemorrhagic stroke [49]. While recent evidence (including a meta-analysis of

31 randomised controlled trials) has disproven this association and demonstrated the safety of statins [41],[49], further work is needed to address patient and clinician concerns.

 OPPORTUNITY

 Develop a targeted education program for ASCVD patients and their treating physicians (outside of cardiac specialties) to address misconceptions about lipid lowering medications.

 OPPORTUNITY

 Conduct an outcomes study to demonstrate the risks and benefits of lipid lowering therapy in Taiwanese people.

A way forward to reduce the burden of ASCVD in Taiwan

Taiwan is at a juncture in how best to lower the burden of ASCVD, both to reduce morbidity and mortality for its citizens and change the disease's trajectory for future generations. Many patients at high risk of a potentially fatal CVD event are young. The tragedy of a premature death deprives a family of a beloved member and Taiwan of a productive citizen who can contribute to the growth and prosperity of the nation.

For most people, ASCVD is preventable and can be easily treated with existing therapies. This report has identified how Taiwan can leverage a population health approach to prevent the onset and/or worsening of ASCVD risk factors.

Key findings

Several areas of opportunity for policy makers in Taiwan were identified in this report:

- Increase public awareness of the importance of hyperlipidemia as a risk factor;
- Increase screening of ASCVD risk factors to enable activation of primary prevention (particularly for younger people who do not qualify for subsidised preventive health checks), in line with clinical guidelines;
- Increase ASCVD training and education for primary care physicians to keep pace with global and national best practice;
 - Improve patient awareness of treatment options for lipid lowering therapies, including the importance of medication compliance;
 - Increase the evidence-base for best practice in ASCVD risk assessment and management in the Taiwanese population;
 - Ensure patient access to advances in clinical care and treatment.

Recommendations

This report presents tailored population health recommendations to address the burden of ASCVD in Taiwan. It has been informed by a thorough literature review, analysis of national and international clinical guidelines for CVD management, and indepth engagement with clinical and policy stakeholders in the ASCVD landscape.

Our recommendations work to significantly reduce ASCVD risk factors among Taiwanese people, and as a result, reduce the prevalence and burden of CVD. Our approach considers all elements that influence clinical decision-making, as well as lifestyle and behavioural approaches to healthy living.

There is an emphasis on better cholesterol management, which represents a substantial population health opportunity. Hyperlipidemia is a preventable, manageable and yet under-treated condition, with a range of effective and low-cost therapies. A multi-faceted population-based approach to managing hyperlipidemia is critical to improve CVD outcomes.

Recommendations at a glance



Detailed recommendations

Our six public health recommendations are described in detail below.

Develop a targeted public health awareness campaign that emphasises the importance of early detection and ongoing treatment of ASCVD risk factors.

With a high prevalence of ASCVD and its risk factors, there remains a continued need for the Taiwan Ministry of Health and Welfare to provide population-level education on ASCVD prevention. Targeted education campaigns should focus on the four risk factors (hyperlipidemia, hypertension, diabetes and smoking) and urge people to take early action to safeguard their health. As part of this, there is a need to elevate the profile of hyperlipidemia as a risk factor to address cholesterol complacency.

Increase screening of ASCVD risk factors in young people to enable activation of primary prevention strategies, in line with clinical guidelines.

The Health Promotion Administration's health screening program provides good coverage of adults aged 40-64. However, the prevalence of CVD is increasing in younger people [22]. While expanding the existing screening program to other age groups is not currently recommended by medical societies [11], there remain valuable opportunities to improve awareness and early detection among younger adults. For example, cholesterol education (and, where indicated, lipid testing) can be offered to young people in primary care visits and via the 12,000+ workplace health promotion programs accredited by the Ministry of Health and Welfare [50].

Develop a strategy for continuous upskilling of primary care physicians on ASCVD to improve compliance with clinical guidelines.

Clinician expertise is a key factor in patient adherence to proven therapies for ASCVD. While cardiac specialists are well placed to stay up-to-date with the latest evidence, there can be a lag effect for primary care physicians and other specialities [20]. An effective way of ensuring consistent treatment approaches and patient advice is for the Government to develop a strategy for the continuous upskilling of primary care physicians on ASCVD. As the primary point of contact for patients, this will enhance quality of care and support timely referrals to specialist care.

Develop a framework for follow-up care that empowers primary care physicians in the ongoing monitoring and management of patients with ASCVD.

Treatment compliance is a known gap in Taiwan, with many ASCVD patients ceasing medication after an initial CVD event [19], [20]. Primary care physicians are well placed to provide patient education, discuss medication concerns, promote healthy lifestyle behaviours and facilitate referrals to specialised services when needed. There is an opportunity to leverage the important role played by primary care physicians in both the monitoring and ongoing management of patients with ASCVD.

Partner with cardiac specialists and medical societies to develop patient education resources on ASCVD prevention and treatment.

Low rates of compliance with prescribed medication for ASCVD is a challenge in Taiwan [20]. Misconceptions about the seriousness of hyperlipidemia and suitable treatment options contribute to poor compliance [48]. With untreated and undertreated ASCVD patients at a higher risk of a CVD event, there is an urgency to provide patients with accurate information on medication safety, side effects and the importance of lifelong medication. Given their respected role in ASCVD care, cardiac specialists and medical societies may be well placed to contribute to development and dissemination of such resources for patients.

Expand patient access to therapies in line with clinical guidelines and global best practice.

The NHI provides comprehensive health coverage for 99.9 percent of people in Taiwan, with subsidised medicines being a key pillar. Statins have been reimbursed since 1995, enabling widespread patient access [20],[16]. However, despite strong evidence for their effectiveness and their inclusion in best practice guidelines [11], advanced therapies for ASCVD have limited availability under the NHI [16]. Control rates of hyperlipidemia are suboptimal with existing treatments, with only 54 percent of ASCVD patients achieving LDL-C targets. There is a need to review NHI funding allocation to ensure ASCVD patients can access the most cost-effective treatments.

The impact of a public health approach to ASCVD

By adopting a population health approach, the Taiwan Government will not only reduce burden of disease, but drastically improve the health of future generations.

To support the recommendations of this report, a discrete event economic model was developed, with evidence-based inputs. Further detail is at Appendix A. Our recommendations have been quantitively assessed against the current burden of CVD in Taiwan and the results are stark.

Lives saved and CVD events avoided

Within the first five years of implementing a population health approach to ASCVD in Taiwan, it is expected that there will be:



19,115 fewer deaths; and



229,385 non-fatal CVD events avoided. The investment in healthcare to achieve this result is an additional NT\$32,031 (USD \$1,070) per patient over the five years, which includes screening tests, healthcare professional costs and lipid lowering therapies. This investment will lead to an annual increase in productivity of NT\$24.6 billion (USD \$821 million) based on the number of deaths and non-fatal CVD events avoided, workforce participation rate (59.19 percent) and average wage (NT\$55,440 per month)

Additionally, the number of patients presenting with CVD events including myocardial infarction, stroke and revascularization procedures will decrease. Each of these events avoided represents a saving to the Government (Figure 7).

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:



793,289 fewer deaths; and



3,187,491 non-fatal CVD events avoided.



Figure 7. Reduction in ASCVD events per 100 patients over five years.

Getting more patients to target

The first step in this population health approach is to identify the number of patients above the recommended target for hyperlipidemia, in particular LDL-C.

Figure 8 below reveals that, in the first five years, the number of ASCVD patients at or

below recommended LDL-C targets increases dramatically with a population health approach. The proportion of patients below 100 mg/dL of LDL-C increases from less than five percent, to almost 30 percent, representing a five-fold increase.



Figure 8. More patients with optimal LDL-C levels with a population health approach.

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Optimising cost-effective treatments

The reason a population health approach presents value for money to Government is that the testing and treatments available are individually cost-effective. Figure 9 reveals the impact of optimising patients using the most appropriate therapy for their LDL-C level, and therefore risk. Our analysis reveals that approximately 30 percent of at-risk patients do not undergo treatment in Taiwan. The recommendations reduce this to less than five percent of the cohort. Utilisation of advanced therapies also increases under our recommended model, which is an important driver of patients achieving a reduction in LDL-C.



Figure 9. Optimising ASCVD therapies with a population health approach.

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

Appendix A Summary of economic model

An economic model for Taiwan 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 lowering therapy.

The approach used to estimate CVD deaths, 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. To ensure robust results that are relevant to a higher risk/ secondary prevention population, the model was calibrated using data from the literature review.

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 this report. The model was populated with relevant indicators and cost data using published data in Taiwan, including cost of events such as myocardial infarction or Ischemic 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 Taiwan.

Appendix B Abbreviations

Abbreviations	Meaning
ASCVD	Atherosclerotic Cardiovascular Disease
ACS	Acute Coronary Syndrome
ACC	American College of Cardiology
АНА	American Heart Association
CVD	Cardiovascular Disease
ESC	European Society of Cardiology
EAS	European Atherosclerosis Society
FH	Familial Hypercholesterolemia
HDL-C	High Density Lipoprotein Cholesterol
LDL-C	Low Density Lipoprotein Cholesterol
NHI	National Health Insurance
PCSK-9	Proprotein convertase subtilisin/kexin type 9
TLGs	Taiwan Lipid Guidelines

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